PRODUCT LICENSING FRAMEWORK III

June 1998

DRAFT

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EXECUTIVE SUMMARY

Product Licensing Framework III enhances the Canadian drug regulatory system by introducing a scheduled post-approval drug assessment program. The licensing framework has two major components:

1. Pre-market drug product categories, product licensing and assignment to post-approval reporting schedules

2. Post-approval reporting schedules and requirements, licence renewal and review of reporting schedule.

Together these two components provide for a continuum of drug product evaluation from the time a product is received as a pre-market submission through to the time the drug product is no longer available on the market.

INTRODUCTION

Background

The concept of a Drug Product Licensing framework for Canada was first proposed in the late 1980's. Dr. Denis Gagnon again raised the concept in his 1992 report, *Working in Partnerships...drug review for the future*. As a result of this report, the Drugs Directorate, now the Therapeutic Products Programme (TPP), adopted and began to implement in August 1993, a renewal strategy to streamline the review and approval process for drugs in Canada. In his report, Dr. Gagnon said that "it is time for us to come out of our traditional model (of drug review), and adopt the more efficient one which will allow us to do the job, within the limits of our resources." and that "an effective program of pharmacovigilance (be developed) as the second major lever of our drug approval system."

One of the outcomes from the implementation of the renewal strategy which responded to many of the recommendations from Dr. Gagnon's report was "A New Drug Licensing Framework for Canada". This document was released by the TPP for comment in January 1996. Following an internal impact assessment and a review of comments received from clients and stakeholders, the document was revised and renamed: Product Licensing Framework (PLF).[1]

In June 1997, an invitational technical workshop was held to gain further input on the scientific content of the document. Comments and input received at this workshop were instrumental in the development of the document - Product Licensing Framework II. A multi-stakeholder consultation workshop on the Product Licensing Framework II was held in October 1997. Comments and feedback received at this workshop are reflected in this latest version of the document - Product Licensing Framework III.

Goals of the Product Licensing Framework

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[1] **The Product Licensing Framework applies only to drug products that are regulated by the Therapeutic Products Programme. Medical devices are not currently included within the scope of the Product Licensing Framework.**

The Product Licensing Framework enhances the drug regulatory process while maintaining the current review standards for safety, quality and efficacy. The goal of the TPP has been to develop a Product Licensing Framework that:

- integrates pre-market and marketed drug assessment into regulatory decision-making
- improves process efficiency
- achieves international harmonization

Features of the Product Licensing Framework

The Product Licensing Framework has two major components:

1. Pre-market drug product categories, product licensing and assignment to post-approval reporting schedule.

2. Post-approval reporting schedules and requirements, licence renewal and review of reporting schedule.

Together, these two components provide for a continuum of drug product evaluation from the time a product is received as a pre-market submission through to the time that the drug product is no longer available on the market.

Within PLF the level of data submission and review for a drug product is linked to the TPP's prior knowledge or experience relating to the safety, quality and efficacy of the product and/or identified product safety, quality or efficacy concerns. Drug products for which the TPP has little or no prior knowledge or experience or products that have identified safety, quality or efficacy issues will have comprehensive data submission requirements and review.

On this basis, PLF groups all drug products into four broad pre-market categories (IV-I) in descending order of data submission requirements and pre-market review. Drug products in Category IV will have comprehensive pre-market data submission requirements and receive intensive pre-market review while drugs in Category I will have minimal pre-market requirements and review. These requirements will ensure that the TPP is provided with the data necessary to make benefit/risk decisions related to the wide spectrum of products it regulates. The introduction in the framework of a scheduled

post-approval assessment program will also ensure that the balance of benefits and risks for a drug product are continually monitored.

Outcomes of Product Licensing

The changes to the drug regulatory process that are proposed in the Product Licensing Framework will enable the Therapeutic Products Programme to:

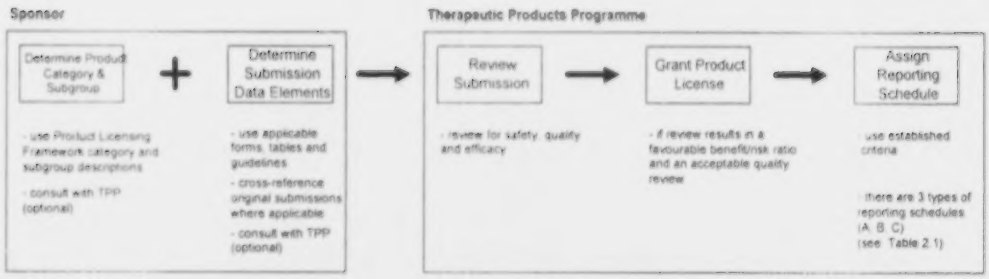
- continually monitor drug products with potential or identified safety, quality or efficacy concerns
- streamline the drug regulatory process and ensure competitive performance targets
- create a transparent process that is easy to understand and provides clear guidance to process participants both internal and external
- harmonize regulatory requirements with those agreed upon internationally
- integrate principles of quality management into the drug regulatory process

Figure 1.1 summarizes the entire continuum of the licensing process and outlines the roles of the drug product sponsor and the TPP. Each of the two major components of the Product Licensing Framework are described in comprehensive detail in this document. An appeals process will be integrated into the licensing process when the framework is implemented. New regulations, policies and guidelines will be developed as required in all areas to support the TPP and drug product sponsors in the implementation of product licensing.

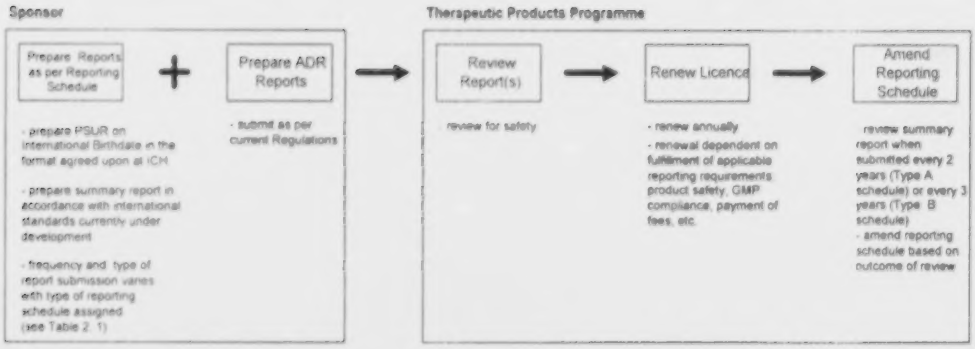
Figure 1.1

Proposed Product Licensing Process

1. Pre-Market


Sponsor
Therapeutic Products Programme
Determine Product Category & Subgroup
Determine Submission Data Elements
- use Product Licensing Framework category and subgroup descriptions
- consult with TPP (optional)
- use applicable forms, tables and guidelines
- cross-reference original submissions where applicable
- consult with TPP (optional)
Review Submission
- review for safety, quality and efficacy
Grant Product License
- if review results in a favourable benefit/risk ratio and an acceptable quality review
Assign Reporting Schedule
- use established criteria
- there are 3 types of reporting schedules (A, B, C) (see Table 2.1)

2. Post Approval


Sponsor
Therapeutic Products Programme
Prepare Reports as per Reporting Schedule
Prepare ADR Reports
- prepare PSUR on International Birthdate in the format agreed upon at ICH
- prepare summary report in accordance with international standards currently under development
- frequency and type of report submission varies with type of reporting schedule assigned (see Table 2. 1)
- submit as per current Regulations
Review Report(s)
- review for safety
Renew Licence
- renew annually
- renewal dependent on fulfillment of applicable reporting requirements product safety, GMP compliance, payment of fees, etc.
Amend Reporting Schedule
- review summary report when submitted every 2 years (Type A schedule) or every 3 years (Type B schedule)
- amend reporting schedule based on outcome of review

SECTION 1 PRE-MARKET

SECTION 1 PRE-MARKET

1.1 Overview of Pre-Market Drug Product Categories

The Product Licensing Framework (PLF) groups all drug products into four broad categories (IV-I). Within PLF, the level of data submission and review for a drug product is linked to the TPP's prior knowledge or experience relating to the safety, quality and efficacy of the product and/or identified product safety, quality or efficacy concerns. Pre-market drug product categories are therefore presented in descending order of data submission requirements and pre-market review. Drug products in Category IV for which the TPP has little or no prior knowledge or experience will have comprehensive data submission requirements and review while drugs in Category I will have minimal pre-market requirements and review. These requirements will ensure that the TPP is provided with the data necessary to make benefit/risk decisions related to the wide spectrum of products it regulates.

The four pre-market categories and some examples of drug products within each category are summarized below:

Category IV - is for a drug product for which there is generally little prior experience or knowledge regarding the safety, efficacy or quality aspects of the active substance(s) or the non-medicinal ingredients. This category has comprehensive data submission requirements and will receive the highest level of pre-market review. Examples of products in this category would be a new active substances and a new propellant in a metered dose inhaler.

Category III - is for a drug product for which there is some prior experience or knowledge regarding the safety, efficacy and quality aspects of the active substance(s) of the drug product. Examples would include a product previously licensed in Canada presented as a new route of administration or new dosage form.

Category II - is for a drug product for which there is extensive prior experience or knowledge regarding the safety, efficacy and quality aspects of the active substance(s). Examples include shampoo for treatment of head lice and many of the marketed cough and cold medicines.

Category I - is for products for which extensive prior knowledge and experience regarding the safety, efficacy and quality aspects of the active substance(s) is available. Products within this category must meet a set of specific criteria in a Class Monograph. Examples of products in this category include: antiperspirants, athletes foot treatments and sunburn protectants.

Each of these four categories is further divided into subgroups based on the active substance, route, form or use of the drug product. This approach to pre-market drug product categorization redefines and clarifies current pre-market groupings. It will replace outdated nomenclature and drug product classifications such as old drug/new drug.

1.2 Overview of Pre-Market Data Submission Requirements

Pre-market data elements which the TPP normally requires to make a benefit/risk decision for a drug product are listed in the tables and forms in section 1.4. Following the description of each category/subgroup in section 1.3, reference is made in a data element box to the applicable tables/forms for that category/subgroup. Where possible, reference is made in the tables and data element boxes to current Therapeutic Products Directorate (TPD) guidelines. The guidelines and tables are to be used together to determine the data submission requirements for a particular drug product. Where applicable, drug product sponsors are encouraged to cross-reference data from a previous submission. Further information on the tables and forms can be found in section 1.4.

The data elements are grouped into five major sections:

- Section I General Pre-market Data Elements
- Section II In Vitro and Animal Studies
- Section III Human Studies
- Section IV Clinical Studies
- Section V Chemistry and Manufacturing Data Elements

The listed data elements are necessarily at the highest common level and may not be applicable to all drug products in a particular category or subgroup. These data elements are intended to be flexible and mirror current TPP requirements. When more than one subgroup applies to a drug product, the requirements for each applicable subgroup must be met.

A listing of TPD Guidelines can be found in Appendix 1 and a Glossary of Terms in Appendix 6. Additional guidelines to assist drug product sponsors in the preparation of drug product submissions will continue to be developed.

1.3 Drug Product Categories: Subgroups and Data Elements

1.3.1 Category IV Products: New Substances

Sponsors must submit a Category IV submission for a drug product when the Therapeutic Products Programme has no prior experience or knowledge regarding the safety, efficacy or quality aspects of the active substance(s) or non-medicinal ingredients. Category IV subgroups represent drug products that contain an active substance or non-medicinal ingredient not previously licensed in a drug product in Canada.

Subgroup IV-1 - new active substance

The product contains a new active substance[2] that is:

a) a chemical, plant[3] or biological substance not previously licensed for sale as a drug in Canada; or,

b) a derivative, isomer or salt of a chemical substance previously licensed for sale as a drug in Canada but differing in properties with regard to safety and/or efficacy, (e.g., the diasteriomers quinine and quinidine); or,

c) a biological substance previously licensed for sale as a drug in Canada which differs in molecular structure, nature of the source material or manufacturing process, and differing in properties with regard to safety and/or efficacy from that previously licensed biological substance.

Data Elements

Use	**Section 1.4:**	**Table 1 - Pre-market Data Elements Sections I, II, III, IV and V**

For subgroup IV-1b, cross-reference data related to safety and efficacy where possible from a previous submission for the original active substance (Sections II, III and IV). Where information in a previous submission does not support, by itself, the safety and/or efficacy of the new

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2 Policy Issues from the Therapeutic Products Directorate, *New Active Substance*; June 4, 1991. 910604.ext

3 Plant substances **not** marketed within the scope of the Therapeutic Products Directorate Guidelines: *Traditional Herbal Medicines* e.g., paclitaxel . See Subgroup II-6 for Traditional Herbal Medicines.

derivative, isomer or salt, bridging studies may have to be submitted to ensure the validity of cross-references.

Subgroup IV-2 - new non-medicinal ingredient

The product contains one or more non-medicinal ingredients (NMI) that have not been previously contained in a drug product licensed for sale in Canada.
(e.g., replacements for CFC propellants in a metered dose inhaler;
polymeric excipients emerging from liposome technology)

Note: The TPP is in the process of developing a policy related to the data submission requirements for new non-medicinal ingredients. As part of this process, the classification of new non-medicinal ingredients within the PLF will be examined. A list of qualified non-medicinal ingredients in Canada will also be developed. The outcome(s) of this policy development exercise will be reflected in updated versions of the PLF.

Data Elements

Use	**Section 1.4:**	**Table 1 - Pre-market Data Elements** **Sections I, II, III, IV and V**

Flexibility on data elements will be considered if there is substantial supportive data that the NMI does not have quality, safety and/or efficacy concerns.

Provide relevant documentation for NMI's that have been qualified in another regulatory jurisdiction or approved for use in food products.

1.3.2 Category III Products: Previously Licensed Substances

Sponsors must submit a Category III submission for a drug product that contains an active substance that has been previously licensed as a drug in Canada. The Therapeutic Products Programme has some prior experience or knowledge regarding the safety, efficacy and quality aspects of the active substance(s) in the drug product, but requires some additional data and information to facilitate a benefit/risk assessment.

Subgroup III-1 - well characterizable biological
The product contains a biological substance that is judged essentially comparable to a biological substance previously licensed for sale as a drug in Canada, but which differs in the nature of the source material or manufacturing process. The substance may not differ significantly in properties with regard to efficacy, although it may differ in respect to safety from that previously licensed biological substance. This subgroup intends to

capture well characterizable biologicals which will receive case-by-case consideration until there is international agreement on possible common standards.

Data Elements

Use	**Section 1.4:**	**Table 1 - Pre-market Data Elements** **Sections I, II, III, IV and V**

For biological products that have been previously licensed:

- cross-reference data where possible from a previous submission (Sections II, III, IV, V).

- where information in a previous submission does not support, by itself, the safety and/or efficacy of the product, bridging studies may have to be submitted to ensure the validity of cross-references.

For biological products that have **not** been previously licensed, but contain an "essentially comparable" active substance that was previously licensed:

- provide sufficient comparative data where possible to prove biocomparability with the previously licensed product. Where this information is not available, complete preclinical and clinical information (Sections II, III and IV) may have to be submitted.

- provide data in Section V - *Chemistry and Manufacturing Data Elements* **to support the different source and production processes.**

Subgroup III-2 - previously licensed substance - new indication
- new dosage regimen
- new route of administration
- new dosage form

The product contains a chemical or biological substance that has been previously licensed for sale in Canada and the product is presented for:

a) a new indication
b) a new dosage regimen
c) a new route of administration; or
d) a new dosage form

Subgroup III-2a - new indication

The product contains a chemical or biological substance that has been previously licensed for sale as a drug in Canada and the product is presented for a new indication.

Data Elements

Use	**Section 1.4:**	**Table 1 - Pre-market Data Elements** **Sections I, II, III, IV and V**

Provide appropriate pre-clinical and clinical data to support the new indication. Where possible, cross-reference data from previous submissions (Sections II, III and IV). **When comparing the previously licensed indication(s) to the new indication, consider whether:**

i) **a new demographic group will be exposed to the active substance;**
ii) **the population will be exposed to lesser or greater amounts of the active substance; and**
iii) **the mode of action and pharmacology of the active substance are different.**

Where data in a previous submission does not support, by itself, safety and efficacy of the drug product for the new indication, bridging studies may have to be submitted to ensure the validity of cross-references.

Cross-reference data from a previous submission for Section V - *Chemistry and Manufacturing Data Elements*

Subgroup III-2b - new dosage regimen

The product contains a chemical or biological substance that has been previously licensed for sale as a drug in Canada and the product is presented for a change to or an extension of the dosage regimen or an additional dosage regimen that has not been previously licensed for that drug product in Canada.

Data Elements

Use	**Section 1.4:**	**Table 1 - Pre-market Data Elements** **Sections I, II, III, IV and V**

Provide appropriate pre-clinical and clinical data to support the new dosage regimen. Where possible, cross-reference data from previous submissions (Sections II, III and IV). When comparing the previously licensed dosage regimen(s) to the new dosage regimen, consider whether:

i) a new demographic group will be exposed to the active substance;

ii) the population will be exposed to lesser or greater amounts of the active substance; and
iii) if the mode of action and pharmacology of the active substance are different.

Where information in a previous submission does not support, by itself, safety and/or efficacy of the new dosage regimen, bridging studies may have to be submitted to ensure the validity of cross-references.

Cross-reference data from a previous submission for Section V - *Chemistry and Manufacturing Data Elements*.

Subgroup III-2c - new route of administration

The product contains a chemical or biological substance previously licensed for sale in Canada and the product is presented for a new route of administration.

Data Elements

Use	**Section 1.4:**	**Table 2--Pre-market Data Elements for Subgroup III-2c: - previously licensed substance - new route of administration Sections I, II, III, IV and V**

Provide appropriate pre-clinical and clinical data to support the new route of administration. Where possible, cross-reference data from previous submissions (Sections II, III and IV). When comparing the previously licensed route(s) of administration to the new route of administration, consider whether:

i) a new demographic group will be exposed to the active substance;
ii) the population will be exposed to lesser or greater amounts of the active substance; and
iii) if the mode of action and pharmacology of the active substance are different.

Where information in a previous submission does not support, by itself, safety and/or efficacy of the new route of administration, bridging studies may have to be submitted to ensure the validity of cross-references.

Cross-reference data from a previous submission for Section V - *Chemistry and Manufacturing Data Elements*.

Subgroup III-2d - new dosage form

The product contains a chemical or biological substance previously licensed for sale in Canada and the product is presented for use in a new dosage form.

Data Elements

Use	**Section 1.4:**	**Table 3--Pre-market Data Elements for Subgroup III-2d: - previously licensed substance - new dosage form Sections I, II, III, IV and V**

Cross-reference data related to safety and efficacy where possible from a previous submission (Sections II, III and IV). Normally bridging studies will be required to ensure the validity of cross-references. More detailed examples of possible data requirements for a previously licensed substance in a new dosage form are provided at the end of Table 3.

If the source and nature of the raw material used in the drug product is identical to that used in another product cross-reference data from a previous submission for Section V - Part A - *Chemistry and Manufacturing Data Elements - Drug Substance.*

Subgroup III-3 - new combination

The product contains two or more chemical or biological substances previously licensed for sale in Canada in a combination that has not been previously licensed for sale in Canada.

Data Elements

Use	**Section 1.4:**	**Table 1 - Pre-market Data Elements Sections I, II, III, IV and V**

Flexibility on data elements will be considered if there is substantial supportive data that the new combination does not have safety, efficacy and/or quality concerns.

Cross-reference data related to safety and efficacy where possible from previous submission(s) for the individual substances. (Sections II, III and IV).

Cross-reference data where possible from previous submission(s) for Section V - *Chemistry and Manufacturing Data Elements.*

Subgroup III-4 - subsequent entry product containing a chemical substance(s) listed on the Biopharmaceutics List[4]

[4] See Subgroup II-2 for subsequent entry products containing a chemical substance **not** listed on the Biopharmaceutics List

The product contains an active substance listed on the Biopharmaceutics List[5] that is contained alone or in combination with another substance(s) in an oral dosage form **where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada. The product must be in one of the following dosage forms:**

i) a solid oral dosage form
ii) an oral suspension
iii) a powder or granules for oral suspension; or

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5 **The Biopharmaceutics List will define active substances for which bioavailability and/or pharmaceutical chemistry problems exist. Comparative bioavailability studies will be required as part of the licensing submission process for drug products containing these substances. For more information on this list refer to Appendix 2.**

iv) an oral solution[6]

Data Elements

Use	**Section 1.4:**	**Table 1 - Pre-market Data Elements** **Sections I, II, III, IV and V**

Provide data to demonstrate that the drug product is comparable in both its safety and efficacy to the Canadian reference product[7]**. Data which demonstrates comparable clinical or pharmacodynamic performance or the bioequivalence of the drug products may be sufficient. Some products may qualify for a waiver of bioequivalence data based on definitive demonstration of pharmaceutical equivalence.**

Provide drug product quality data in Section V- Chemistry and Manufacturing Data Elements.

Subgroup III-5 - subsequent entry product containing a substance of plant origin

The product contains an active substance that is a plant or of plant origin previously licensed for sale in Canada and not marketed within the scope of the Therapeutic Products Directorate Guidelines*: Traditional Herbal Medicines*.[8]

Data Elements

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6 Policy Issues from the Therapeutic Products Directorate: *Waiver of Comparative Bioavailability Studies for Oral Solutions*, October 10, 1996

7 Policy Issue from the Therapeutic Products Directorate: *Canadian Reference Product*, December 5, 1995.

8 See Subgroup II-6 for Traditional Herbal Medicines

Use	Section 1.4:	Table 1 - Pre-market Data Elements Sections I, II, III, IV and V

Provide data to demonstrate that the drug product is comparable in both its safety and efficacy to the previously licensed product. If bioequivalence of the proposed and previously licensed products cannot be established, comparable pharmacodynamic performance or clinical efficacy must be demonstrated.

Provide data related to botanical characterization and test procedures in Section V- *Chemistry and Manufacturing Data Elements* to demonstrate that the quality of the drug product does not differ from that of the previously licensed product.

Subgroup III-6 - prescription to non-prescription switch

The product contains a chemical or biological substance previously licensed for sale in Canada and the product is presented for a prescription to non-prescription switch.

Data Elements

Use	Section 1.4:	Table 4 - Factors Affecting Changes in Schedule F Status
and	Health Protection Branch Information Letter No. 781 - *Prescription to Nonprescription Switches*, June 28, 1990.	

Table 4 outlines the ten factors and three exceptions to be considered in regard to the listing of substances on Schedule F to the *Food and Drug Regulations*. Drug products containing substances listed on Schedule F cannot be sold to the general public without a prescription. These factors relate to the use, safety and effects of the drug product, and the disease treated by the drug product and must be addressed in a submission for a prescription to non-prescription switch.

Information Letter No. 781 outlines the data requirements for submissions to remove drugs for human use from Schedule F and outlines internal mechanisms for handling these submissions.

If proposed non-prescription drug product is identical to the current prescription drug product, cross-reference data where possible from previous submissions. As described in IL No. 781, additional data will be required in areas where the proposed non-prescription drug product differs from the current prescription drug product.

Subgroup III-7 - subsequent entry products in other dosage forms

The product contains an active substance in one of the following dosage forms where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada:

a) a modified release dosage form;
b) a solution for inhalation;
c) a suspension or powder for inhalation;
d) an injectable preparation, which may or may not be intended for use as a solution;
e) a peritoneal dialysis solution;
f) a hemodialysis solution;
g) an ophthalmic preparation;
h) a rectal suppository that delivers the active substance systemically through absorption;
i) a topical, dental topical, vaginal or nasal preparation intended for local effect;
j) an otic preparation; or
k) a dermal topical that delivers the active substance systemically through absorption

Note: Some products within these subgroups may qualify for waiver of bioequivalence data based on definitive demonstration of pharmaceutical equivalence [9,10]***. However, comparative***

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9 Policy Issues from the Therapeutic Products Directorate: *Submissions for Generic Topical Drugs*, September 24, 1990 (900924.ext)

pharmacodynamic, clinical or bioavailability studies may be required to establish the relative safety and efficacy in relation to the Canadian reference product if pharmaceutical equivalence cannot be established.

10 Policy Issues from the Therapeutic Products Directorate: *Submissions for Generic Parenteral Drugs*, March 1, 1990 (900301 ext)

Subgroup III-7a modified release dosage form[11]

Data Elements

Use	Section 1.4:	Table 1--General Pre-market Data Elements Sections I, III, IV and V
and	Therapeutic Products Directorate Guidelines: *Preparation of Drug Identification Submissions,* February 22, 1995 - Section VIII	

Provide data that the drug product is comparable in both its safety and efficacy to the Canadian reference product. Data which demonstrates comparable clinical or pharmacodynamic performance or the bioequivalence of the drug products may be sufficient.

If the source and nature of the active substance used in the drug product is identical to that used in another drug product licensed by the sponsor, cross-reference data from a previous submission for Section V - Part A - *Chemistry and Manufacturing Data Elements - Drug Substance.* Depending on the nature of the dosage form, physico-chemical characteristics and methods of manufacturing of the drug product, additional drug substance information may be necessary.

Subgroup III -7b solution for inhalation

Data Elements

Use	Section 1.4:	Table 1--General Pre-market Data Elements Sections I, III, IV and V
and	Therapeutic Products Directorate Guidelines: *Preparation of Drug Identification Submissions,* February 22, 1995 - Section IX	

11 *see*: Subgroup III-2d for a modified release dosage form which has not been previously licensed in Canada

Provide data to demonstrate that the drug product is comparable to the Canadian reference product. It may be sufficient to submit *in vitro* test data only. Pharmacodynamic or clinical studies may be required where comparative physical and *in vitro* testing are inadequate to demonstrate the safety and efficacy of the drug product.

Subgroup III-7c suspension or powder for inhalation

Data Elements

Use	**Section 1.4:**	**Table 1--General Pre-market Data Elements Sections I, IV and V**
and	Therapeutic Products Directorate Draft Guidelines: *In Vivo Test Requirements for Second Entry Metered Dose Inhalers*, September 1992	
and	Therapeutic Products Directorate Draft Guidelines: *Metered Dose Inhalers*, November 1992	

An adequate link between *in vitro* test data and the clinical safety and efficacy of these drug products has not been established.

Provide data to demonstrate that the drug product is comparable to the Canadian reference product. Provide both *in vitro* and clinical data. Provide data from product specific tests comparing the drug product to the Canadian reference product including:

a) comparative chemical analysis to demonstrate equivalent qualitative and quantitative composition

b) comparative physico-chemical tests including osmolality, surface tension and droplet size

Subgroup III-7d injectable preparation, may or may not be intended for use as a solution

Data Elements

Use	Section 1.4:	Table 1--General Pre-market Data Elements Sections I, III, IV and V
and	Therapeutic Products Directorate Guidelines: *Preparation of Drug Identification Submissions,* February 22, 1995 - Section X	
and	Policy Issues from the Therapeutic Products Directorate: *Submissions for Generic Parenteral Drugs,* March 1, 1990 (900301.ext)	

Provide data that the drug product is the same or pharmaceutically equivalent to the Canadian reference product or provide comparative pharmacodynamic and clinical studies.

Subgroup III-7e peritoneal dialysis solution

Data Elements

Use	Section 1.4:	Table 1--General Pre-market Data Elements Sections I and V
and	Therapeutic Products Directorate Guidelines: *Preparation of Drug Identification Submissions,* February 22, 1995 - Section XI	

Subgroup III-7f hemodialysis solution

Data Elements

Use	**Section 1.4:**	**Table 1--General Pre-market Data Elements Sections I and V**
and	Therapeutic Products Directorate Guidelines: *Preparation of Drug Identification Submissions,* February 22, 1995 - Section XII	
and	Therapeutic Products Directorate Class Monograph: *Haemodialysis Solutions*, October 9, 1996	

Subgroup III-7g ophthalmic preparation

Data Elements

Use	**Section 1.4:**	**Table 1--General Pre-market Data Elements Sections I, III, IV and V**
and	**Therapeutic Products Directorate Guidelines: *Preparation of Drug Identification Submissions,* February 22, 1995 - Section XIII**	

Provide data that the drug product is the same or pharmaceutically equivalent to the Canadian reference product. Provide comparative pharmacodynamic and clinical studies. Artificial tears, eye washes and contact lens solutions are excluded from the requirement to determine equivalence.

Provide drug product quality data in Section V - *Chemistry and Manufacturing Data Elements*

Subgroup III-7h rectal suppository that delivers the active substance systemically

Data Elements

Use	Section 1.4:	Table 1--General Pre-market Data Elements Sections I, III, IV and V
and	Therapeutic Products Directorate Guidelines: *Preparation of Drug Identification Submissions*, February 22, 1995 - Section XIV	

Provide data that the drug product is the same or pharmaceutically equivalent to the Canadian reference product. If the active substance in this dosage form is on the Biopharmaceutics List, provide data from comparative pharmacodynamic, clinical or bioavailability studies to establish the safety and efficacy of the product in relation to the Canadian reference product.

Provide drug product quality data in Section V - *Chemistry and Manufacturing Data Elements*

Subgroup III-7i topical preparation, dental topical, vaginal or nasal preparation intended for local effect

Data Elements

Use	Section 1.4:	Table 1--General Pre-market Data Elements Sections I, III, IV and V
and	Therapeutic Products Directorate Guidelines: *Preparation of Drug Identification Submissions*, February 22, 1995 - Section XV	
and	Policy Issues from the Therapeutic Products Directorate: *Submissions from Generic Topical Drugs*, September 24, 1990 (900924.ext)	

Provide comparative pharmacodynamic and clinical studies that establish the comparative safety and effectiveness between the drug product and the Canadian reference product.

Provide drug product quality data in Section V - *Chemistry and Manufacturing Data Elements*

Subgroup III-7j otic preparation

Data Elements

Use	**Section 1.4:**	**Table 1--General Pre-market Data Elements** **Sections I, III, IV and V**
and	**Therapeutic Products Directorate Guidelines: *Preparation of Drug Identification Submissions*, February 22, 1995 - Section XV**	

Provide data that the drug product is the same or pharmaceutically equivalent to the Canadian reference product or provide comparative pharmacodynamic and clinical studies.

Provide drug product quality data in Section V - *Chemistry and Manufacturing Data Elements*

Subgroup III-7k dermal topical that delivers the active substance systemically

Data Elements

Use	**Section 1.4:**	**Table 1--General Pre-market Data Elements** **Sections I, III, IV and V**

Provide data that the drug product is the same or pharmaceutically equivalent to the Canadian reference product. If the active substance in this dosage form is on the Biopharmaceutics List, provide data from comparative pharmacodynamic, clinical or bioavailability studies to establish the safety and efficacy of the product in relation to the Canadian reference product. Provide data from irritation and sensitization studies.

Provide drug product quality data in Section V - *Chemistry and Manufacturing Data Elements*

1.3.3 Category II Products: Subsequent Entry Products Drug Products with Labelling Standards

Sponsors must submit a Category II submission for a drug product for which the Therapeutic Products Programme has extensive prior experience or knowledge regarding the safety, efficacy and quality aspects of the active substance(s). There are published Labelling Standards for many of the drug products in this category.[12]

Subgroup II-1 - subsequent entry product - new indication
- change/extension of indication
- change/extension of dosage regimen

The product contains a chemical or biological substance previously licensed for sale in Canada and the product is presented for:

a) a new indication; or
b) a change to or an extension of an existing indication; or
c) a change to, an extension of or an additional dosage regimen,

and where that indication or dosage regimen has been previously licensed for that active substance in Canada.

Data Elements

Use	**Section 1.4 :**	**Form A - Drug Submission Application**

12 **It is the intention of the Therapeutic Products Programme to develop additional labelling standards where applicable, for drug products within this category. In the interim and when labelling standards do not exist, limited data submission will continue to be required.**

Subgroup II-2 - subsequent entry product containing a chemical substance not listed on the Biopharmaceutics List[13]

The product contains a chemical substance *not* listed on the Biopharmaceutics List that is contained alone or in combination with another substance(s) in an oral dosage form where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada. The product must be in one of the following dosage forms:

i) **a solid oral dosage form;**
ii) **an oral suspension;**
iii) **a powder or granules for oral suspension;**
iv) **an oral solution.**

Data Elements

Use	**Section 1.4:**	**Table 1 - Pre-market Data Elements** **Section V- *Chemistry and Manufacturing Data Elements***
and	**Section 1.4:**	**Form A: Drug Submission Application**

Note: Specific data elements from Section V - *Chemistry and Manufacturing Data Elements* that would be necessary to support the submissions for this subgroup are currently under development in the TPP. Until finalized, some elements from Table 1, Section V- may apply.

Subgroup II-3 - products with Labelling Standards

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13 See Subgroup III-4 for a subsequent entry drug product containing a chemical substance listed on the Biopharmaceutics List.

The product meets the criteria of a published Labelling Standard. See Appendix 3 for a list of Labelling Standards.[14]

Data Elements

Use	**Section 1.4:**	**Form A - Drug Submission Application**

Sponsors must also provide a letter quoting the name and date of the Labelling Standard referenced; indicating compliance with or outlining any discrepancies from the Labelling Standard, with supporting rationale. In the case of discrepancies, further data may be requested.

Subgroup II-4 - hard surface disinfectant

The product contains a chemical substance that is represented for use as a disinfectant for use on inanimate environmental surfaces in health care facilities, food processing establishments or for use on medical devices where the product does not meet the criteria of a published Labelling Standard or Class Monograph.

Note: the regulatory framework for disinfectants is currently being restructured to include disinfectants and antimicrobials in all areas of use.

Data Elements

Use	**Section 1.4:**	**Form A - Drug Submission Application**
and	**Therapeutic Products Directorate Guidelines*: Disinfectant Drugs*, Cat. No. H42-2/61-1994**	

Subgroup II-5 - traditional herbal medicine

14 Products which meet the criteria of Labelling Standards prepared for prescription to nonprescription switches must comply with the Labelling Standard and the data elements of the applicable subgroup in Category III.

The product contains an active substance that is a plant or of plant origin and intended to be marketed within the scope of the Therapeutic Products Directorate Guidelines: *Traditional Herbal Medicines*.

Note: the regulatory framework for natural health products is currently under review.

Data Elements

Use	**Therapeutic Products Directorate Guidelines: *Traditional Herbal Medicines*, Cat. No. H42-2-36-1990**

Subgroup II-6 - homeopathic preparation

The product contains an active substance that is intended to be marketed as a Homeopathic Medicine within the scope of the Therapeutic Products Directorate Guidelines: *Homeopathic Preparations: Application For Drug Identification Numbers*.

Note: the regulatory framework for natural health products is currently under review.

Data Elements

Use	**Therapeutic Products Directorate Guidelines: *Homeopathic Preparations: Application For Drug Identification Numbers*, Cat. No. 42-2-21-1990**

Subgroup II-7 - radiopharmaceutical kit

The drug product is a commercial radiopharmaceutical prepared from an approved kit.
(e.g., a Tc-99m medronate injection prepared from medronate kit and dispensed into vials or unit dose syringes)

Data Elements

Provide stability data if the drug product is dispensed into vials or unit-dose syringes

Provide information on the vials and syringes used

1.3.4 Category I Products: Drug Products with Class Monographs

Sponsors must submit a Category I Drug Submission Certification for a drug product when the Therapeutic Products Programme has extensive prior knowledge and experience regarding the safety, efficacy and quality aspects of the active substance(s). Class Monographs have been developed for drug classes in this category. Data submission requirements will be satisfied by the sponsor's attestation to conformance with a Class Monograph. A drug product must meet all of the following criteria to qualify for this category:

- **The drug product is indicated for the prevention or relief of minor self-limiting conditions or their symptoms;**
- **The intended use will not delay recognition of serious ailments;**
- **The drug product has not been associated with clinically significant and/or a high incidence of adverse effects;**
- **The drug product contains only therapeutically rational substances and no medicinal substance superfluous to the treatment for which it is intended;**
- **The drug product has no significant potential for accidental poisoning or misuse. Misuse should not result in a significant health hazard;**
- **Directions for use are simple, uncomplicated and easy to follow;**
- **Cautionary statements, if required, are minor in nature and scope; and**
- **Appropriate selection and use of the drug product do not require the intervention of a health professional.**

Category I Monographs	Latest Revision
Acne Therapy	September 11, 1995
Antidandruff Products	September 11, 1995
Antiperspirants	September 11, 1995

Antiseptic Skin Cleansers	**September 11, 1995**
Athletes Foot Treatments	**September 11, 1995**
Contact Lens Disinfectants	**November 15, 1995**
Dietary Mineral Supplements	**May 28, 1997**
Dietary Vitamin Supplements	**May 28, 1997**
Fluoride Containing Anti-caries Products	**October 10, 1995**
Hard Surface Disinfectants	**November 15, 1996**
Medicated Skin Care Products	**September 11, 1995**
Sunburn Protectants	**May 1, 1997**
Throat Lozenges	**January 13, 1995**
Toilet Bowl Disinfectant Cleaners	**April 10, 1996**

Data Elements

Use	**Section 1.4:**	**Form B: Category I Drug Submission Certification**

1.4 Tables and Forms

1.4 Tables and Forms

This section contains the tables and forms referenced in the data element boxes for the drug product categories and subgroups outlined in section 1.3. There are 4 tables and 2 forms.

Table 1 - Pre-Market Data Elements, lists the relevant data elements for a Category IV submission. The data elements listed in the tables are necessarily at the highest common level and may not be applicable to all drug products in a particular category or subgroup.

Where possible, reference has been made both in the tables and data element boxes in section 1.3 to current Therapeutic Products Directorate guidelines. A listing of TPD Guidelines can be found in Appendix 1. The guidelines and tables should be used together to determine the data submission requirements for a particular drug product. Data submission requirements are intended to be flexible and mirror current TPP requirements. Where possible, drug product sponsors are encouraged to cross-reference data from a previous submission. Additional guidelines to assist sponsors in the preparation of drug product submissions will continue to be developed

To avoid repetition, there are instances in Tables 2 and 3 where only the title of a section is listed. When this occurs, sponsors should refer to Table 1 for guidance in determining the data elements applicable to that section. For example, in Table 2 - Section I, General Data Elements is listed without subheadings. Sponsors should refer to Table 1 and ensure that all the data elements listed under the subheadings to Section I are provided with their submission. This requirement may be fulfilled by providing the necessary data with the submission or by cross-referencing the data element to a previous submission.

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SECTION 1.4: TABLE 1
PRE-MARKET DATA ELEMENTS[15,16]

I GENERAL DATA ELEMENTS
A. FOREIGN STATUS
1. Countries where the drug is marketed
a. Indications/route of administration/number of years marketed
2. Countries where the drug was submitted for approval
a. Date of filing and status
i) pending
ii) withdrawn
iii) refused
b. Reasons and dates - where applicable
3. Countries where the prescribing information (labelling) was changed after approval
a. Dates and reasons for changes
4. Package inserts from all countries where the drug has been approved
5. List of completed and in-progress studies
B. CANADIAN STATUS
1. List of prior related submissions
a. INDs (by objectives and/or indications)
b. Completed studies

15 Therapeutic Products Directorate Guidelines: *Preparation of Human New Drug Submissions*, Cat. No. H42-2-38-1990

16 Therapeutic Products Directorate Guidelines: *Preparation of Human New Drug Submissions*, Cat. No. H42-2-38-1998E-IN

c. In-progress studies (i.e. for other indications)
i) studies included in the submission
ii) other studies
2. Other related submissions (i.e., NDS, S/NDS, Master Files, etc.)
3. Special Access Programme summary
C. PROPOSED LABELLING[17]
1. Product Monograph[18]
2. Package Insert
3. Draft Labels
II IN VITRO AND ANIMAL STUDIES
A. PHARMACOLOGY
1. General Pharmacology
a. In-Vitro Studies
i) receptor binding assays
ii) levels and turnovers of neurotransmitters and their metabolites
iii) biochemical pathways to determine potential mechanism of action
b. In-Vivo Studies
i) actions related to predicted therapeutic activity, secondary activity

17 Therapeutic Products Directorate Guidelines: *Labelling of Drugs for Human Use*, Cat. No. H42-2-2-1989

18 Therapeutic Products Directorate Guidelines: *Product Monographs (Amendment May 1990)*, Cat. No. H42-2-12-1989

ii) actions related to safety
iii) results of broad screening
2. Other Effects
a. Tolerance/ Tachyphylaxis/ Supersensitivity
b. Rebound/Withdrawal Effect
c. Dependence Liability - where applicable
B. PHARMACOKINETICS/TOXICOKINETICS
1. Absorption/ Distribution/ Metabolism/ Excretion (ADME)
a. Drug distribution
b. Tissue/fluid levels
c. Blood/brain barrier
d. Placental/milk transfers
e. Effect of route of administration on ADME
2. Comparative Pharmacokinetics/ toxicokinetics
a. Interspecies
b. Animal vs human
c. Comparative ADME (animal vs human)
3. Enzyme Induction/ Inhibition
4. Microsomal Isozyme(s)
5. Other
C. TOXICOLOGY[19]
1. Single dose toxicity (acute toxicity)

19 Therapeutic Products Directorate Guidelines: *Toxicological Evaluation (revised with ICH Inserts)*, Cat. No. H42-2/15-1990E

2. Multiple dose toxicity (subchronic, chronic toxicity)
3. Carcinogenicity
4. Mutagenicity
5. Reproduction/Teratology (may include neurotoxicity in special cases)
6. Special studies - where applicable
a. Neurotoxicity
b. Hepatotoxicity
c. Nephrotoxicity
d. Immunotoxicity
e. Irritation
f. Antigenicity
g. Phototoxicity
h. Photocarcinogenicity
i. Joint toxicity
j. Old vs young animals
k. Ototoxicity
l. Special studies
m. Other studies
7. Environmental impact studies - where applicable to meet requirements under other relevant legislation (i.e., handling and disposal of drug; manufacturing processes)
D. MICROBIOLOGY
1. Sensitivity - clinical and laboratory
a. Static
b. Cidal

c. Effects on activity
i) inoculum
ii) culture media
iii) biological fluids
iv) pH
2. Mechanism of action
3. Mechanism of resistance
4. Post-antibiotic effect
5. Interaction with other antibiotics
6. Susceptibility test methods
7. In-vivo animal models
8. Metabolism by organisms
9. Other - where applicable
III HUMAN STUDIES
A. CLINICAL PHARMACOLOGY
1. Pharmacokinetics
a. Absorption/ distribution/ metabolism/ excretion (ADME)
i) drug distribution
ii) tissue/fluid levels
iii) blood/brain barrier
iv) placental/milk transfer
v) effect of route of administration on ADME
b. Comparative pharmacokinetics (animal vs human)
c. Enzyme induction/ inhibition

d. Microsomal isozyme(s)
e. Population kinetics
f. Kinetics regarding age/gender/race[20]
g. Kinetics in organ impaired (renal, hepatic) patients
h. Disease/drug interaction studies
i. Drug/drug interaction studies
j. Food/drug interaction studies
k. Special studies
l. Other studies - where applicable (i.e., dosimetry calculations for radiopharmaceuticals)
2. Pharmacodynamics
a. Single dose tolerance studies
b. Multiple dose tolerance studies
c. Disease/drug interaction
d. Drug/drug interaction
e. Food/drug interaction
f. Special population studies[21]
g. Other studies
3. Bioavailability[22,23,24,25,26]

20 Therapeutic Products Directorate Guidelines: *Inclusion of Women in Clinical Trials*, April 17, 1997.

21 Therapeutic Products Directorate Guidelines: *ICH - Studies in Support of Special Populations: Geriatrics* (Cat. No. H42-2/67-1-1994E)

22 Therapeutic Products Directorate Guidelines: *Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations Used for Systemic Effects*, Cat. No. H42-2-/56-1992

23 Therapeutic Products Directorate Guidelines: *Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B: Oral Modified Release Formulations*, Cat. No.H42-2/73-1996E

IV CLINICAL STUDIES[27,28]
A. DOSE RANGING STUDIES[29]
B. MAJOR STUDIES
1. Short term studies
a. Controlled studies
b. Open studies
c. Other studies - where applicable (i.e., irritation, sensitization)
2. Long term studies
a. Efficacy studies
i) Controlled studies
ii) Open studies
b. Safety studies
i) Controlled studies
ii) Open studies

24 Therapeutic Products Directorate Guidelines: *Preparation of Drug Submissions: Comparative Bioavailability Studies*, Cat. No. H42-2/74-1997E

25 Therapeutic Products Directorate Publications: *Report C: Report on Bioavailability of Oral Dosage Formulations not in Modified Release Form of Drugs Used for Systemic Effects, Having Complicated or Variable Pharmacokinetics*, Expert Advisory Committee on Bioavailabililty, Health Protection Branch, December 1992

26 Policy Issue from the Therapeutic Products Directorate: *Bioequivalence of Proportional Formulations - Solid Oral Dosage Forms*, March 7, 1996

27 Therapeutic Products Directorate Guidelines: *ICH - Good Clinical Practice: Consolidated Guideline*, Cat. No. H42-2/67-11-1997E

28 Therapeutic Products Directorate Guidelines: *ICH - Structure and Content of Clinical Study Reports*, Cat. No. H42-2/67-10-1996E

29 Therapeutic Products Directorate Guidelines: *ICH - Dose Response Information to Support Drug Registration*, Cat. No. H42-2/67-4-1994E

c. Other studies - where applicable
C. SPECIAL STUDIES (Related to disease and/or concomitant therapies)
D. ON-GOING STUDIES (Progress report on safety (ADR, dropouts, etc.)
E. OTHER STUDIES - where applicable (i.e., gender/age/race specfic studies; quality of life studies; dosimetry calculations for radiopharmaceuticals)
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS [30,31]
A. DRUG SUBSTANCE
1. Pharmacopeial/ Reference Text Status
2. Structural Relationship to Other Drugs of Similar Structure
3. Nomenclature
4. Source
5. Method of Manufacture
6. Development Chemistry
7. Impurities[32]
8. Reference Standard
9. Control Tests on the Drug Substance
10. Batch Analyses
11. Packaging
12. Stability[33]

30 Therapeutic Products Directorate Guidelines: *Chemistry and Manufacturing: New Drugs*, Cat. No. H42-2-30-1990

31 Policy Issues from the Therapeutic Products Directorate: *Help Guide on the Preparation of a Comprehensive Summary of Chemistry and Manufacturing Information and a Certified Product Information Document for New Drugs (Non-Schedule D)*, June 30, 1995 (300695.ext)

32 Therapeutic Products Directorate Guidelines: *ICH - Impurities in New Drug Substances*, Cat. No. H42-2/67-6-1995E

B. DRUG PRODUCT
1. Pharmacopeial Status
2. Production Site
3. GMP Status
4. Developmental Pharmaceutics
5. Formulation and Method of Manufacture
6. Excipients
7. Control Tests on the Finished Drug Product
8. Batch Analyses
9. Primary Packaging
10. Stability[33]

33 Therapeutic Products Directorate Guidelines: *ICH - Stability Testing of New Drug Substances and Products*, Cat. No. H42-2/67-3-1994E

SECTION 1.4: TABLE 2
PRE-MARKET DATA ELEMENTS FOR SUBGROUPS III-2c
- previously licensed substance - new route of administration

	Oral - Injectable Injectable - Oral	Oral / Injectable to another for systemic or local use
I GENERAL DATA ELEMENTS		
II IN VITRO AND ANIMAL STUDIES		
A. PHARMACOLOGY		
1. General Pharmacology		
b. In-Vivo Studies		
i) actions related to predicted therapeutic activity		
ii) actions related to safety		
B. PHARMACOKINETICS/TOXICOKINETICS		
1. Absorption/ Distribution/ Metabolism/ Excretion (ADME)		
e. Effect of route of administration on ADME		
2. Comparative Pharmacokinetics/ toxicokinetics		
c. Comparative ADME (animal vs human)		
C. TOXICOLOGY		
2. Multiple dose toxicity (subchronic, chronic toxicity)		
5. Reproduction/Teratology (may include		

neurotoxicity in special cases)		
6. Special studies - where applicable (i.e., irritation studies, sensitization)	Local toxicity for injectables	Local toxicity for local use products
7. Environmental impact studies - where applicable to meet requirements under other relevant legislation (i.e., handling and disposal of drug; manufacturing processes)		
III HUMAN STUDIES		
A. CLINICAL PHARMACOLOGY		
1. Pharmacokinetics		
a. Absorption/ distribution/ metabolism/ excretion (ADME)		
i) effect of route of administration on ADME		
b. Comparative pharmacokinetics (animal vs human)		
g. Kinetics in organ impaired (renal, hepatic) patients		
i. Drug/drug interaction studies		
j. Food/drug interaction studies	Only for products for oral administration	
2. Pharmacodynamics		
a. Single dose tolerance studies		
b. Multiple dose tolerance studies		
e. Food/drug interaction	Only for products for oral	

	administration	
IV CLINICAL STUDIES		
A. DOSE RANGING STUDIES		
B. MAJOR STUDIES		
1. Short term studies		
a. Controlled studies		
b. Open studies		
c. Other studies - where applicable (i.e., irritation, sensitization)		
2. Long term studies		
a. Efficacy studies		
i) Controlled studies		
ii) Open studies		
b. Safety studies		
i) Controlled studies		
ii) Open studies		
c. Other studies - where applicable		
C. SPECIAL STUDIES (Related to disease and/or concomitant therapies)		
D. ON-GOING STUDIES (Progress report on safety ADR, dropouts, etc.)		
E. OTHER STUDIES -where applicable (i.e., gender/age/race specific studies)		
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS		
A. DRUG SUBSTANCE		

B.	DRUG PRODUCT		

SECTION 1.4: TABLE 3
PRE-MARKET DATA ELEMENTS
PRODUCTS in SUBGROUP III-2d
previously licensed substance - new dosage form*

**examples of possible data requirements for a previously licensed substance in a new dosage form are provided at the end of this table*

I GENERAL DATA ELEMENTS
II IN VITRO AND ANIMAL STUDIES
A. PHARMACOLOGY
1. General Pharmacology
b. In-Vivo Studies
i) actions related to predicted therapeutic activity
ii) actions related to safety
B. PHARMACOKINETICS/TOXICOKINETICS
1. Absorption/ Distribution/ Metabolism/ Excretion (ADME)
a. Drug distribution
b. Tissue/fluid levels
e. Effect of route of administration on ADME
C. TOXICOLOGY
7. Environmental impact studies - where applicable to meet requirements under other relevant legislation
III HUMAN STUDIES
A. CLINICAL PHARMACOLOGY
1. Pharmacokinetics

a. Absorption/ distribution/ metabolism/ excretion (ADME)
i) drug distribution
ii) tissue/fluid levels
v) effect of route of administration on ADME
b. Comparative pharmacokinetics (animal vs human)
g. Kinetics in organ impaired (renal, hepatic) patients
h. Disease/drug interaction studies
i. Drug/drug interaction
j. Food/drug interaction
2. Pharmacodynamics
a. Single dose tolerance studies
b. Multiple dose tolerance studies
c. Disease/drug interaction
d. Drug/drug interaction
e. Food/drug interaction
f. Special population studies
g. Other studies
IV CLINICAL STUDIES
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS
A. DRUG SUBSTANCE
B. DRUG PRODUCT

Examples of possible data requirements for a previously licensed substance in a new dosage form:

tablet to capsule change: provide comparative data to support the safety and effectiveness of the new drug product. Data should demonstrate the relative clinical effectiveness, the relative pharmacodynamic performance or the bioequivalence of the two drug products.

oral tablet dosage form to a modified release dosage form: provide bridging studies to ensure the validity of the original toxicology data under Section II; fulfil much of Section III to validate the new dosage form; and demonstrate the clinical effectiveness of the new product under Section IV.

topical solution to topical cream (intended for local effect): demonstrate efficacy by clinical data; demonstrate that the original toxicology is valid for the new drug product; dermal irritation and dermal sensitization studies may also be needed to support the new dosage form as may comparative studies measuring relative absorption of the drug products.

injectable dosage form to a topical patch delivery system: an irritation study and sensitization study along with a comparative pharmacokinetic study which demonstrates similar systemic dosing from the original dosage form and from a topical dermal patch delivery system may be sufficient as a bridge to the safety and efficacy data base submitted on the original dosage form.

SECTION 1.4: TABLE 4
SUBGROUP III-6 - prescription to nonprescription switch
FACTORS AFFECTING CHANGES IN SCHEDULE F STATUS

Factors used to determine whether this level of control over the sale of these drugs is appropriate
1. They require individualized instructions and/or direct practitioner supervision, adjunctive therapy with scheduled drugs or routine laboratory monitoring.
2. There exists a narrow margin of safety between the therapeutic and toxic dosages, especially in populations such as geriatrics, children and pregnant/nursing mothers.
3. They possess the potential or are known to cause undesirable or severe side effects at normal therapeutic dosage levels.
4. They are known by experimental data to induce toxicity in animals but have not been in clinical use for a sufficient period of time to establish the pattern or the frequency of long-term toxic effects in humans.
5. They are indicated for serious disease states often misdiagnosed by the public.
6. Their use may mask other ailments.
7. They have contributed to or are likely to contribute to the development of resistant strains of micro-organisms in humans.
8. They possess a sufficient dependence or abuse potential that has led or is likely to lead to harmful non-medical use if distribution is not supervised.
9. They possess a potentially high level of risk relative to their expected benefits.
10. They have a therapeutic effect based on recently elucidated pharmacologic concepts, the consequences of which have not been adequately established.
Exceptions
1. Drugs which are required to be readily available under emergency circumstances where it is not practical to obtain a prescription (such as adrenalin in insect-bite kits).
2. Drugs which are rarely used without a practitioner's supervision, and where the need for free availability outweighs the need for protection under Schedule F (such as insulin and nitroglycerin).

3. Drugs which have the potential to produce dangerous interactions with other drugs or food constituents but effective labelling can minimize this risk.

Form A: Drug Submission Application

Health Canada Santé Canada

DRUG SUBMISSION APPLICATION

The Drug Submission Application is designed to assist manufacturers and sponsors in submitting information required to initiate the evaluation of any one of the following types of submissions:

- Drug Identification Number (DIN) Application,
- New Drug Submission (NDS),
- Supplemental New Drug Submission (S/NDS)
- Notifiable Change (N/C) Submission,
- Cross Referenced to NDS or S/NDS (C/REF) Submission, or
- Investigational New Drug (IND) Submission.

Form A is to be completed for all submission types. Only one formulation and formulation strength should be included per copy of this form.

If this form has been previously completed and a Project ID number assigned, additional or supplementary information for a submission need only be accompanied by a covering letter that includes:

- the drug name(s)
- the Project ID number
- whether the information was requested by Therapeutic Products Directorate, and
- a brief description of the attached information

Form B, C, D, or E is to be completed in addition to Form A, depending on the type of submission. DIN Applications require only the completion of Form A.

Completion Instructions for Form A may be found by turning the complete forms package over. Completion instructions for specific submission types (Forms B, C, D, E) may be found at the bottom of each form.

All shaded fields are for Health Protection Branch (HPB) use only.

FORM A - GENERAL INFORMATION

PART 1 - Manufacturer / Sponsor Information

1. Type of Submission	2. Number of Volumes	**HPB Use Only:**	3. Project ID	4. Category	5. Status

Manufacturer / Sponsor

6. Code	7. Name

8. Street No. and Name	9. City/Town	10. Prov./State	11. Country	12. Postal/ZIP Code

Contact Person

13. Name	14. Title	15. Tel. No.	16. FAX No.	. Language ☐ English Preferred ☐ French

Mailing Address	☐ Same as above	☐ See below		
18. Street No. and Name	19. City/Town	20. Prov./State	21. Country	22. Postal/ZIP Code
Canadian Distributor	☐ Same as manufacturer/sponsor	☐ Same as Mailing Address	☐ See below	

23. Name				
24. Street No. and Name	25. City/Town	26. Prov.	27. Country	28. Postal Code
Other Name and Address on Label				
29. Name				
30. Street No. and Name	31. City/Town	32. Prov./State	33. Country	34. Postal/ZIP Code

Responsible Bureau (HPB Use Only)					
35. Code	36. Name	37. Code	38. Name		
39. CR Date D M Y	40. CR File No.	41. Prov./State	42. Kit ☐Yes ☐No	43. Parent ID No.	
44. Product Name		45. Name Type	46. Schedule		
47. Proper or Common Name					

48. Related Submissions (referred to in this submission)

Type	Project ID No.	Product Name	Manufacturer / Sponsor Name	Notes

HPB 3011 (3-91)

PART 2 - Formulation Information on this Submission

49. Proposed Expiry / Shelf Life ____ years _____ months

50. Medicinal Ingredients

Ingredient Name	Standard	Strength	Units	Pe	Calculated as Base?
					☐ Yes ☐ No
					☐ Yes ☐ No

☐ Yes ☐ No

☐ Yes ☐ No

☐ Yes ☐ No

Attach separate sheets (same format) if necessary. Number of pages attached: _____

51. Non-medicinal ingredients (include colouring agents)

Ingredient Name	Standard	Strength	Units	Per

Attach separate sheets (same format) if necessary. Number of pages attached: _____

52. Specify the dosage form

53. Package Sizes available

54. Therapeutic Classification

55. Specify the Route(s) of administration

. Use of Drug ☐ Human ☐ Veterinary Use (see 60 - 62)

☐ General Disinfectant (inanimate objects only) ➢ ☐ hospital ☐ food processing ☐ instruments

57. Recommended Purpose

58. Recommended Dosage

59. Draft of Proposed Canadian Label and Package Insert enclosed? ☐ Yes ☐ No

Complete for Veterinary Products only

60. Species Recommended for use

_____

_____

_____

_____

_____

_____

61. Used for treatment of food-producing animals ☐ Yes ☐ No

62. Withdrawal Time

Species	Days	Hours

63. Name of Authorized Signing Official	64. Title	65. Signature	66. Date D | M | Y

Form B: Category I Drug Submission Certification

We certify that: **Product Name:**

1. The information and data provided in support of this submission is complete and accurate and, where summarized, correctly represents the information and material to which it refers.

2. The product will be manufactured in accordance with Canadian Good Manufacturing Practices (GMP) as required under Division 2 of the Food and Drug Regulations.

3. Stability data will support the labelled expiration date of the product. In addition to the first two production batches of the product, stability will be monitored in accordance with Canadian GMP requirements.

4. The product does **not** contain any of the following ingredients:

   a) phenacetin in combination with any salt or derivative of salicylic acid;

   b) oxyphenisatin;

   c) oxyphenisatin acetate;

   d) phenisatin;

   e) strychnine or any of its salts;

   f) extracts or tinctures of:
      i) *Strychnos nux vomica*
      ii) *Strychnos Ignatii*
      ii) a *Strychnos* species containing strychnine, other than those species mentioned in subparagraph i) and ii);

   g) Methapyrilene or any of its salts;

   h) Echimidine or any of its salts;

   i) any of the following plant species or extracts or tinctures thereof:
      i) *Symphytum asperum*
      ii) *Symphytum X uplandicum*
      iii) any other plant species containing echimidine;

   j) mercury or a salt derivative thereof;

   k) chloroform;

   l) arsenic or any of its salts or derivatives;

   m) methyl salicylate (as a medicinal ingredient in a drug for internal use).

5. The product does not contain any colouring agent, with the exception of those listed in Section C.01.040.2 of the Food and Drug Regulations (this does not apply to hard surface or instrument disinfectants).

6. If the product contains animal tissue or animal tissue was used as an intermediate during manufacturing, complete the Animal Tissue Form attached to the relevant Category I Monograph.

7. The product named in this application will comply in all respects with the requirements of Category I Monograph

   Name of Monograph:

   Date of Monograph:

8. The product named in this application will comply with published Therapeutic Products Directorate guidelines and policies.

9. Signature of the responsible officer of the company certifying the accuracy of this document

_____
Signature Date

_____
Name Position / Title

Company

September 12, 1995

Revised: May, 1998

1.5 Product Licensing and Assignment to Post-Approval Reporting Schedule

1.5 Product Licensing and Assignment to Post-Approval Reporting Schedule

The licensing process and assignment of post-approval reporting schedules is presented in this section. For specific details on post-approval reporting schedules and reporting requirements, refer to section 2.1, Post-Approval Reporting Schedules and Requirements.

At the conclusion of the pre-market review, a favourable benefit/risk ratio will result in the issuance of a licence to market the drug product. At that time, the product will be assigned to one of three (schedule A, B or C) post-approval reporting schedules which determine the reporting requirements that must be fulfilled while the drug is being marketed (*see:* Table 2.1).

Reporting Schedule A entails the most comprehensive post-approval report and review requirements. Reporting Schedule B entails a moderate level of post-approval report and review requirements and Reporting Schedule C entails a minimal level of post-approval report and review requirements.

Those drug products containing new substances, (pre-market Category IV) will be automatically assigned to reporting schedule A. This will link the level of post-approval data submission and review to the TPP's amount of knowledge or experience about the drug product in the marketplace. If the sponsor wishes to have a product containing a new substance considered for assignment to a less frequent reporting schedule, the sponsor must provide the TPP with a scientific rationale prior to the issuance of the license to support an alternative assignment. This rationale must include international post-approval information from populations and therapeutic applications which are comparable to the drug product's intended use in Canada. A decision to assign the drug product to a particular post-approval reporting schedule will then be based on a review of this information in conjunction with the results from the pre-market submission review.

The movement of a drug product from A to B or B to C reporting schedules is likely to occur upon completion of the reporting period for that schedule. New drug products containing the same active substance as a previously licensed drug product will normally be assigned to the same reporting schedule as the previously licensed product. The TPP will have to provide a scientific rationale to justify the retention of a product in a particular reporting schedule or the movement of a product to a more frequent reporting schedule. (*see:* sections 2.5.1, 2.5.2).

The TPP will adopt the international birthdate[34] as the standard "reference point" for the reporting of information on a drug product. This will harmonize the reporting of post-approval information internationally and facilitate the simultaneous submission to the TPP of post-approval reports for drug products containing the same active substance. For combination products containing active

34 International Birthdate: the date of the first marketing authorization for the product granted to any company in any country in the world.

substances in two different reporting schedules, the combination product will be assigned to the reporting schedule with the most comprehensive requirements.

1.5.1 License with Conditions

The TPP may issue a License with Conditions for a drug product that is subject to Category IV pre-market requirements **and also** meets the requirements of the Policy on Priority Review.[35] For more information on License with Conditions refer to: Policy from the Therapeutic Products Programme, Notice of Compliance with Conditions (NOC/C), May 28, 1998.

[35] **Policy Statement from the Therapeutic Products Directorate, Priority Review of Drug Submissions, December 13, 1996**

SECTION 2 POST-APPROVAL

SECTION 2: POST-APPROVAL

2.1 Post-Approval Reporting Schedules and Requirements

This section describes the post-approval reporting schedules and requirements. For specific information on the assignment of drug products to post-approval reporting schedules, refer to section 1.5, Product Licensing and Assignment to Post-Approval Reporting Schedule.

The post-approval reporting schedules (A, B or C) determine the reporting requirements that must be fulfilled while a drug product is being marketed in Canada (*see:* Table 2.1). The level of post-approval data submission and review in the reporting schedules is linked to the Therapeutic Products Programme's (TPP) amount of knowledge or experience about the drug product in the marketplace and/or potential or known product concerns identified during the review process. The introduction in the framework of a scheduled post-approval assessment program will ensure that the balance of benefits and risks for a drug product is continually monitored.

Sponsors will continue to report serious expected and unexpected adverse drug reactions (ADR) to the TPP. A new activity under product licensing is the scheduled preparation and submission of Periodic Safety Update Reports (PSUR).[36] (*see*: section 2.2.1) For products assigned to reporting schedules A and B, the PSUR will replace the current requirement for the preparation of an annual ADR summary report. The preparation of annual ADR summary reports will still be a requirement for drug products in schedule C.

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36 Previously referred to as CIOMS II (Council for International Organizations of Medical Sciences) and currently incorporated into ICH document E2C: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. The content of this safety report has been the subject of international discussion and has been agreed upon at ICH. (*see*: Appendix 4)

Sponsors will be required to have in place, a Product Change Control System. This system will ensure that changes to drug products are properly documented, evaluated and authorized by qualified personnel prior to implementation. (*see*: section 2.2.4)

At the completion of the reporting period for a drug product, sponsors will prepare and submit to the TPP a Product/Substance Summary Report. For drug products in schedules A and B, a favourable review of this report will result in the movement of the drug product to a less frequent reporting schedule. (*see*: section 2.2.3)

This approach to post-approval surveillance is consistent with regulatory approaches in the U.S. and Europe. (*see*: Appendix 5) These reporting schedules should permit multi-national sponsors to be able to submit one report simultaneously to the necessary regulatory authorities. It will also ensure that resources for post-approval reviews are focused on those products with potential or identified safety concerns.

2.1.1 Reporting Schedules: General Overview

Table 2.1 details the post-approval activities following issuance of a product licence including: reporting schedules, required reports, reporting frequency and review of reporting schedule. Sponsors will be expected to monitor their products in accordance with the requirements of the reporting schedule assigned to their product. For a description of the required post-approval reports, refer to section 2.2, Post-Approval Reports. For a complete description of post-approval reporting requirements, refer to section 2.3, Post-Approval Reporting Requirements.

Table 2.1: Reporting Schedule; Required Reports and Frequency; Review of Reporting Schedule

LICEN	Reporting Schedule	Required Safety Report	Reporting Frequency - Preparation - Submission	ADR Reporting	Review of Reporting Schedule
	A	PSUR	- prepare and submit every 6 months	continue to submit serious expected and unexpected ADR's as per current regulations PSUR to replace current annual	2 yr
	B	PSUR	- prepare and submit annually		3 yr

C				reports	
E	C	Upon identification of issue of concern , sponsor will submit a report focusing on issue under investigation	- prepare and submit summary report every 5 years	Continue annual reports as per current Schedule 844 requirements - summary line listing - critical analysis - evaluation of recommended actions	5 yr

2.2 Post-Approval Reports

Sponsors will be responsible for preparing and submitting to the TPP the applicable post-approval reports for each of their licensed drug products. Sponsors will not be precluded from co-operating with other sponsors in the preparation of a report on a particular active substance. The TPP will adopt the international birth date[37] as the standard "reference point" for the reporting of information on a drug product. This will harmonize the reporting of post-approval information at the international level.

There are three post-approval reports:

a) Periodic Safety Update Report (PSUR)
b) Adverse Drug Reaction (ADR) Summary Report
c) Product/Substance Summary Report

Sponsors must also have in place a Product Change Control System.

2.2.1 Periodic Safety Update Report (PSUR)

The Periodic Safety Update Report (PSUR) provides information on the world-wide safety experience with an active substance at specific times following its approval for use. The report will allow a comprehensive safety profile of an active substance to be developed during its first years of availability on the commercial market. The format and content of this report has been agreed upon by the International Conference on Harmonization (ICH).

Sponsors of drug products assigned to post-approval schedules A and B will be required to prepare and submit PSURs to the TPP in the format described in the ICH guideline. (*see*: Appendix 4) All dosage forms and formulations as well as indications for a given pharmacologically active substance should be covered in one PSUR from a sponsor. Accordingly, the PSUR for an active substance, will cover several drug products from a single sponsor. Where applicable, cross-referencing of reports is encouraged. For drug products assigned to reporting schedules A and B, the PSUR will replace the current requirement for the preparation of an annual adverse drug reaction (ADR) summary report.

2.2.2 Adverse Drug Reaction (ADR) Summary Report

Health practitioners, including, physicians, pharmacists, nurses and dentists are encouraged to voluntarily report suspected adverse drug reactions to the TPP. This practice remains a viable

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37 International Birthdate: the date of the first marketing authorization for the product granted to any company in any country in the world.

means of detecting rare and previously unknown reactions to drugs when they are used in general practice settings following their approval for use.

Drug product sponsors must report all serious domestic and all serious unexpected foreign ADR's to the TPP within 15 calendar days of receipt of the report. Sponsors of drug products assigned to reporting schedule C will continue to conduct an annual critical analysis of adverse drug reactions to their products. This information is to be submitted in the form of an annual summary report to the TPP upon request. Sponsors should refer to the Therapeutic Products Programme's *Guidelines for Reporting Adverse Reactions to Marketed Drugs*[38] for further information on these requirements.

2.2.3 Product/Substance Summary Report

At the completion of the reporting period for a drug product, sponsors will prepare and submit to the TPP a Product/Substance Summary Report. This report will cover the entire previous reporting period and for products in reporting schedules A and B, form the basis for the TPP's review of the drug product's reporting schedule. (*see*: section 2.5)

The format and content of the Product/Substance Summary Report has not yet been defined. This issue is under discussion internationally and is likely to be resolved by the time product licensing is implemented. The TPP will harmonize the reporting requirements for drug product sponsors under this section with the outcomes of these discussions.

2.2.4 Product Change Control System

Sponsors must have a Product Change Control System in place to ensure that changes to drug products are properly documented, evaluated and authorized by qualified personnel prior to implementation. Documentation should include a description of and, where appropriate, the rationale for the change, as well as the associate supporting data or information and authorization. This information will be maintained on site and submitted to the TPP upon request.

In light of the number and cumulative effect of changes possible over the life of a product, companies should assure themselves that product or formulation creep does not lead to differences in product safety or efficacy.

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38 Therapeutic Products Programme Guidelines: *Guidelines for Reporting Adverse Reactions to Marketed Drugs*, Cat. No. H49-106-1996E

2.3 Post-Approval Reporting Requirements

2.3.1 Schedule A Reporting Requirements

Data Elements

Periodic Safety Update Report - prepare and submit to the TPP every 6 months or when monitoring identifies concern
Product/Substance Summary Report - prepare and submit to the TPP at 2 years

Periodic Safety Update Report
Submit within 60 days of the international birthdate for the drug product.

Product/Substance Summary Report
A favourable review will facilitate movement to a less frequent reporting schedule.

2.3.2 Schedule B Reporting Requirements

Data Elements

Periodic Safety Update Report - prepare and submit to the TPP annually or when monitoring identifies concerns
Product/Substance Summary Report - prepare and submit to the TPP at 3 years

Periodic Safety Update Report
Submit within 60 days of the international birthdate for the drug product.

Product/Substance Summary Report
A favourable review will facilitate movement to a less frequent reporting schedule.

2.3.3 Schedule C Reporting Requirements

Data Elements

Adverse Drug Reaction Summary Report - prepare annually and submit to the TPP upon request
Product/Substance Summary Report - prepare and submit to the TPP at 5 years

Adverse Drug Reaction Summary Report
Sponsors must notify the TPP when a significant safety, quality or effectiveness issue is identified during the course of this annual monitoring activity.

If information becomes available indicating possible problems with the safety, quality or effectiveness of a drug product, sponsors will be required to submit within 30 days of request by the TPP, a report which focuses on the

issue under investigation. Depending on the scope of the issue, an alternate time frame for preparation and submission of such a report may be negotiated.

2.3.4 Notification and Reporting on Specific Issues of Concern

In addition to the reporting requirements outlined above, sponsors will be required to:

a) **Notify** the TPP within 5 days when, on the basis of safety or quality concerns, an expert panel or advisory committee has been struck in a foreign jurisdiction to address an issue or when there has been significant regulatory action in another jurisdiction including a direction to issue warnings, a health advisory or the removal of a product from the market.

b) **Prepare and submit a report** on the issue that prompted the action in the foreign jurisdiction. The report should be available to the TPP within 30 days of the notification. This time frame may be subject to negotiation with the TPP when the scope of the issue under investigation warrants additional time to gather the necessary information.

c) **Prepare and submit a report** within 30 days of request by the TPP when a signal/alert is raised in Canada. This time frame may be subject to negotiation with the TPP when the scope of the issue under investigation warrants additional time to gather the necessary information.

2.3.5 Effectiveness Data

The efficacy of a drug product is determined from evidence gathered from adequate and well-controlled clinical trials. It is well recognized that the therapeutic outcome in a real world patient population (effectiveness) may differ from the efficacy determined in controlled clinical trials. Accordingly, effectiveness issues may arise only when a drug product is widely marketed. The TPP may request data related to the effectiveness of a drug product when data from post-approval reports indicates a potential lack of efficacy.

2.4 Licence Status

2.4.1 Annual Licence Renewal

Drug product licenses will be renewed annually. This will replace the current annual DIN notification. The renewal of the licence will be subject to the fulfilment of applicable regulatory requirements. A drug product licence **will not** be renewed if:

- Product safety concerns are identified;
- **Post-approval reporting requirements are not met;**
- **GMP and other regulatory requirements including fee requirements are not met; or**

- Problems identified during post-approval assessment cannot be resolved.

2.4.2 Suspension/Revocation/Amendment of a Licence

The TPP will have the authority to suspend, revoke or amend a drug product licence should public health concerns become apparent or the sponsor fails to meet the post-approval reporting requirements or other regulatory requirements for the drug product. When appropriate, drug products may be made available to specified individuals through the Special Access Program (SAP) until such licencing issues are resolved.

2.5 Review of Reporting Schedule

The reporting schedule assigned to a drug product will be reviewed at the completion of the reporting period. The TPP will perform a comprehensive assessment of the data submitted in the Product/Substance Summary Report to determine if the product's original benefit/risk analysis remains valid. If the licence holder has presented information that alters the validity of the original benefit/risk assessment, the licence holder may have to make changes to the product, product labelling or other parameters before the Programme renews the licence. Based on the outcome of the review, a decision will be made as to whether the reporting schedule should be retained or amended to reduce or increase the reporting requirements.

2.5.1 Movement to a Less Frequent Reporting Schedule

The movement of products from A to B or B to C reporting schedules is likely to occur upon completion of the reporting period. The TPP must provide a scientific rationale to justify the retention of a product in a particular reporting schedule. There may be instances when the reporting period was not long enough to gather sufficient safety information on a product with very limited exposure. In such instances, a particular reporting schedule may need to be extended in order to more fully establish the post-approval safety profile of the drug.

2.5.2 Movement to a More Frequent Reporting Schedule

In some instances, a drug product may be moved from a lower post-approval reporting schedule to a more frequent reporting schedule. A drug product will be considered for assignment to a more frequent reporting schedule should public health concerns related to the product become apparent.

2.6 Multiple Product (Class, Group) Assessment

Issues may arise that will warrant the assessment of an entire group of drug products. The grouping of drug products in this instance will vary with the issue under investigation. In some instances, the same pharmacological grouping will be appropriate. In other cases the group may be comprised of products within the same therapeutic class, chemical group or all products used for a particular indication. The intent of a group assessment will be to focus on reviewing the appropriate group of products that are relevant to a particular safety issue. Group assessments and how to resolve issues related to the confidentiality of proprietary information given the need to generate the necessary data will be further defined.

2.7 Product Monograph Updates

The introduction of a scheduled post-approval assessment program will facilitate the regular updating of Product Monographs. As the result of the outcome of a group assessment, the TPP may require changes to the Product Monographs of all products involved in the assessment.

2.8 Changes to Marketed Drug Products

Sponsors of drug products with changes other than those subject only to notification must file a licence amendment application containing the data and information specified within the pre-market category and subgroup applicable to the change. For example, if a sponsor applies for a new indication for a drug product, the submission requirements of Category III-2a will apply and the sponsor will need to submit the data necessary to support the change. The TPP will review the reporting schedule prior to issuing a new product licence. Depending on the nature of the change to the product, post-approval reporting requirements could increase, decrease or remain the same as the original reporting schedule.

Sponsors will market a drug product under one reporting schedule only. The TPP will have the authority to cancel a previous licence with a specific reporting schedule once a new licence with a new reporting schedule is issued for a product.

2.9 Implementation & Marketed Drug Products

When product licensing is implemented, the TPP will issue a licence with a reporting schedule to all marketed drug products. Drug products containing a particular active substance should be assigned to the same reporting schedule. Products will be assigned to post-approval

reporting schedules on the following basis unless the TPP provides a scientific rationale for the assignment of the drug product to a more stringent reporting schedule.

Drug products containing an active substance which has been approved for use in Canada for less than 2 years will be assigned to reporting schedule A. Drug products containing an active substance which has been approved for use in Canada for more than 2 years but less than 5 years will be assigned to reporting schedule B. Drug products containing an active substance which has been approved for use in Canada for more than 5 years will be assigned to reporting schedule C. For combination products containing active substances in two different reporting schedules, the combination product will be assigned to the reporting schedule with the most comprehensive requirements.

Sponsors will be responsible for prospectively preparing and submitting to the TPP the applicable post-approval reports for each of their licensed drug products.

APPENDICES

APPENDIX 1:

Therapeutic Products Directorate Guidelines and Publications

Therapeutic Products Directorate Guidelines and Publications
(available through the Canadian Government Publishing Centre)

ORDER FORM

Catalogue No.	Title	Price	Quantity	Amount
H42-2-18-1990	Glossary of Terms	$ 5.95		
H42-2-2-1989	Labelling of Drugs for Human Use	$11.95		
H42-2-14-1989	Conduct of Clinical Investigations (Addendum Sept. 1991)	$6.75		
H42-2-12-1989	Product Monographs (Amendment May 1990)	$10.25		
H42-2-1-1989	Good Manufacturing Practices, 3rd Edition	$24.75		
H42-2-21-1990	Homeopathic Preparations: Application for Drug Identification Numbers	$10.00		
H42-2-25-1990	Completing an Application for Registration as a Proprietary Medicine	$11.50		
H42-2/15-1990E	Toxicological Evaluation (revised with ICH Inserts)	$32.95		
H42-2-36-1990	Traditional Herbal Medicines	$6.95		
H42-2-32-1990	Manufacture and Testing of Monoclonal Antibodies and Their Conjugates	$6.95		
H42-2-33-1990	Utilization of Continuous Cell Lines in the Manufacture of Biologics	$6.95		
H42-2-34-1990	Manufacture and Testing of Biologics Produced by Recombinant DNA Technology	$6.95		
H42-2-3-1990	Consumer Drug Advertising (Amendment October 1991)	$14.95		
H42-2-30-1990	Chemistry and Manufacturing: New Drugs	$12.50		
H42-2-37-1990	Preparation of Investigational New Drug Submissions	$8.95		
H42-2-38-1990	Preparation of Human New Drug Submissions	$7.95		
H49-5-1991E	Health Protection and Drug Laws	$9.95		
H42-2-53-1992	Inspection of Biologics Manufacturers	$8.95		
H42-2-55-1992	The Lot by Lot Testing and Release Programme	$4.50		
H42-2-11-1992	Labelling of Cosmetics	$9.95		
H42-2/49-1992	Blood Collection and Blood Component Manufacturing	$9.95		

H42-2-2-17	Cover and Spine Inserts for Binder	$2.50		
H42-2/31-1994	Product Master Files	$13.95		
H42-2/60-1994	Directions for Use of Estrogen-Progestin Combination Oral Contraceptives (OCs)	$ 7.95		
H42-2/61-1994	Disinfectant Drugs	$9.95		
H42-2/63-1994	Acceptable Methods	$15.95		
H42-2/67-4-1994E	ICH - Dose-Response Information to Support Drug Registration	$ 8.95		
H42-2/67-3-1994E	ICH - Stability Testing of New Drug Substances and Products	$ 9.95		
H42-2/67-1-1994E	ICH - Studies in Support of Special Populations: Geriatrics	$ 6.95		
H42-2/67-1995E	Menopause	$14.95		
H42-2/68-1995E	Oral Contraceptives 1994 (the report and guidelines are included together)	$14.95		
H42-2/67-8-1995E	ICH - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting	$13.95		
H42-2/67-7-1995E	ICH - The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions	$ 7.95		
Catalogue No.	Title	Price	Quantity	Amount
H42-2/67-6-1995E	ICH - Impurities in New Drug Substances	$13.95		
H49-106-1996E	Guidelines for Reporting Adverse Reactions to Marketed Drugs (Vaccines excluded)	$11.95		
Order Value Fee $00.01 - $05.00 = $ 2.25 $25.01 - $75.00 = $ 5.45 Over $200.00 = 6% (of total order value)	Order Value Fee $05.01 -$ 25.00 = $ 3.50 $75.01 -$200.00 = $10.50	Shipping & Handling (fee extra)		
All sales are final; prices are subject to change without notice.		TOTAL		

APPENDIX 2:

The Biopharmaceutics List

The Biopharmaceutics List

The Biopharmaceutics List will define active substances for which bioavailability and/or pharmaceutical chemistry problems exist. Comparative bioavailability studies will be required as part of the licensing submission process for drug products containing these substances.

The Therapeutic Products Programme (TPP) is in the process of creating the Biopharmaceutics List. A consultant's report proposing a number of criteria to be considered in adding or deleting drugs from the Biopharmaceutics List will be posted on the TPP website for comment by stakeholders in June 1998.

Initially, the list will be based on:

- drugs currently requiring the submission of an Abbreviated New Drug Submission (ANDS);
- all new active substances as they receive a Notice of Compliance
- the criteria in the Final Report, D-09: Drug Identification Number, September 1994. These criteria remain valid, subject to consultation, revision and further definition as elaborated in the above mentioned report.

Other factors regarding the Biopharmaceutics List:

- listing of an ingredient will not be dependent on the ingredient being on a federal schedule.
- an ingredient will remain on the list unless a sponsor petitions for its removal. An advisory panel convened by the TPP will review the petition. The TPP will publish the agenda of the advisory panel in advance, permit additional parties to submit data in support of or against the petition and hold meetings that would be open to the public; and
- the TPP will make the list and assessment critieria available to all stakeholders through the TPP website.

APPENDIX 3:

List of Labelling Standards

List of Labelling Standards

Labelling standard	Latest Revision
Analgesics (includes acetaminophen, salicylates, +ibuprofen, codeine)	December 2, 1994
Anorectal Drug Products	September 1, 1994 *
Antacid	July 24, 1996
Anthelmintics	May 17, 1996
Antiflatulents	July 19, 1996
Antifungals (topical)	January 30, 1995 *
Antifungal (Naftifine & Imidazole)	October 22, 1993
Bismuth Subsalicylate	May 17, 1996
Caffeine	September 22, 1992
Chamomile	May 17, 1996
Corn and Callous Removers	May 17, 1996
Counterirritants	September 1, 1994 *
Cyproheptadine	August 14, 1992
Dental and Oral Care Products For Professional Use	March 19, 1997
Dimenhydrinate	December 1, 1994
Echinacea Root	June 1, 1997
Ephedra	July 17, 1996
Ephedrine	July 17, 1996
Ethylene Oxide Gaseous Sterilant	September 5, 1995
+Famotidine	August 20, 1997
Feverfew Leaf	August 6, 1997
Fluoride-Containing Treatment Gels and Rinses	March 19, 1997
For Consumer Use	March 19, 1997
Homeopathic Preparations	May 7, 1997 *
Hydrocortisone	April 11, 1991
Intestinal Flora Modifiers	June 5, 1995
+Intravaginal (Miconazole & Clotrimazole)	December 1, 1994
Laxatives (general)	September 1, 1994 *
a. Bulk Forming	
b. Carbon Dioxide Releasing	
c. Hyperosmotic	
d. Kit Bowel Cleansing System	October 3, 1997
e. Lactulose	
f. Lubricant	
g. Saline	
h. Stool Softener	
i. Stimulant	October 3, 1997
Lindane Lotion - Scabicide	December 12, 1989
Lindane Shampoo - Pediculicide	December 12, 1989
Mineral Supplements	December 6, 1996*
+Nicotine Gum	May 17, 1997
+Nicotine Patches	November 12, 1997
+Non-Classical Antihistamines	April 1, 1998
Oral Potassium Supplements	December 2, 1994
Peppermint	May 17, 1996
Peroxide Oral Care Products	September 29, 1995

Poison Treatment	September 1, 1994 *
Quaternary Ammonium Compounds for Use Against HIV	October 10, 1995
Sleep Aids	July 12, 1993
Topical - Anaesthetic/Analgesic/Antipruritic	September 1, 1994 *
Topical Antibiotics	November 19, 1992 *
Triethanolamine Salicylate (Trolamine)	September 13, 1995
Ubiquinone	September 1, 1994 *
Valerian	May 17, 1996
Vitamin Supplements	January 24, 1995 *
Wart Removers	September 1, 1994 *

(April 1, 1998)

* Bioavailability assessment not required
(see Item 8. DIN Submission Certification Form)

\+ Labelling Standards prepared for prescription to nonprescription switches. Products which meet the criteria of these Labelling Standards must comply with the Labelling Standard and the data elements of the applicable subgroup in Category III.

APPENDIX 4:

ICH Harmonized Tripartite Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

DRAFT

Periodic Safety Update Reports

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH Harmonized Tripartite Guideline

CLINICAL SAFETY DATA MANAGEMENT:

PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

Recommended for Adoption
at Step 4 of the ICH Process
on 6 November 1996
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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DRAFT

CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

ICH Harmonised Tripartite Guideline

Having reached *Step* 4 of the ICH Process at the ICH Steering Committee meeting on 6 November 1996, this guideline is recommended for adoption to the three regulatory parties to ICH

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CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

1. INTRODUCTION

1.1 Objectives of the Guideline

The main objective of ICH is to harmonize technical requirements for registration or marketing approval. However, because new products are introduced at different times in different markets and the same product may be marketed in one or more countries and still be under development in others, reporting and use of clinical safety information should be regarded as part of a continuum.

The regulatory requirements, particularly regarding frequency of submission and content of periodic safety updates, are not the same in the three regions (EU, Japan, USA). In order to avoid duplication of effort and to ensure that important data are submitted with consistency to regulatory authorities, this guideline on the format and content for comprehensive periodic safety updates of marketed medicinal products has been developed.[39]

1.2 Background

When a new medicinal product is submitted for marketing approval, except in special situations, the demonstration of its efficacy and the evaluation of its safety are based at most on several thousand patients. The limited number of patients included in clinical trials, the exclusion at least initially of certain patients at-risk, the lack of significant long-term treatment experience, and the limitation of concomitant therapies do not allow a thorough evaluation of the safety profile. Under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible.

In order to develop a comprehensive picture of clinical safety, medicinal products should be closely monitored, especially during the first years of commercialization. Surveillance of marketed drugs is a shared responsibility between Regulatory Authorities and Marketing Authorization Holders (MAH). They record information on drug safety from different sources and procedures have been developed to ensure timely detection and mutual exchange of safety data. Because all information cannot be evaluated with the same degree of priority, regulatory authorities have defined the information to be submitted on an

[39] Guidelines are not legally binding. Some portions of this guideline may not be reflected in existing regulations. To that extent, until the regulations are amended, MAHs must comply with existing regulations.

expedited basis; in most countries this rapid transmission is usually focused on the expedited reporting of adverse reactions that are both serious and unexpected.

Reevaluation of the benefit/risk ratio of a drug is usually not possible for each individual ADR case, even if serious. Therefore, Periodic Safety Update Reports (PSUR) present the world-wide safety experience of a medicinal product at defined times post-authorization, in order to:

- report all the relevant new safety information from appropriate sources
- relate these data to patient exposure
- summarize the market authorization status in different countries and any significant variations related to safety
- create periodically the opportunity for an overall safety reevaluation
- indicate whether changes should be made to product information in order to optimize the use of the product.

However, if the PSURs required in the different countries where the product is on the market require a different format, content, period covered and filing date, MAH would be required to prepare on an excessively frequent basis different reports for the same product. In addition, under such conditions, different regulators could receive different kinds and amounts of information at different times. Thus, efforts are needed to harmonize the requirements for PSURs, which will also improve the efficiency with which they are produced.

The current situation for periodic safety reports on marketed drugs is different among the three ICH regions. For example:

- The US regulations require quarterly reports during the first 3 years, then annual reports. The FDA has recently published proposed rules[40] which take into account the CIOMS Working Group II proposals[41].

- In the EU, Council Directive 93/39/EEC and Council Regulation 2309/93 require reports with a periodicity of 6 months for two years, annually for the three following years and then every five years, at time of renewal of registration.

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40 Adverse Experience Reporting Requirements for Human Drug and Licensed Biological Products; Proposed Rule, Federal Register, 27 October 1994, pp. 54046-54064.

41 International Reporting of Periodic Drug-Safety Update Summaries. Final Report of CIOMS Working Group II. CIOMS - Geneva 1992

- In Japan, the authorities require a survey on a cohort of a few thousand patients established by a certain number of identified institutions during the 6 years following authorization. Systematic information on this cohort, taking into account a precise denominator, must be reported annually. Regarding other marketing experience, adverse reactions which are non-serious, but both mild in severity and unlabeled must be reported every 6 months for 3 years and annually thereafter.

Following a discussion of the objectives and general principles for preparing and submitting PSURs, a model for their format and content is presented. Appended is a glossary of important relevant terms.

1.3 Scope of the Guideline

This guideline on the format and content of periodic safety update reports (PSURs) is considered particularly suitable for comprehensive reports covering short periods (e.g. six months, one year) often prepared during the initial years following approval/authorization.

This guideline might also be applicable for longer term reporting intervals; however, other options may be appropriate.

1.4 General Principles

1.4.1 One report for one active substance

Ordinarily, all dosage forms and formulations as well as indications for a given pharmacologically active substance should be covered in one PSUR. Within the single PSUR, separate presentations of data for different dosage forms, indications or populations (e.g. children vs. adults) may be appropriate.

For combinations of substances also marketed individually, safety information for the fixed combination may be reported either in a separate PSUR or included as separate presentations in the report for one of the separate components, depending on the circumstances. Cross-referencing all relevant PSURs is considered important.

1.4.2 General scope of information

All relevant clinical and non-clinical safety data should cover only the period of the report (interval data) with the exception of regulatory status information on authorization applications and renewals, as well as data on serious, unlisted ADRs (*see*: section 1.4.5), which should be cumulative.

The main focus of the report should be adverse drug reactions (ADRs). For spontaneous reports, unless indicated otherwise by the reporting health-care professional, all adverse experiences should be assumed to be adverse drug reactions; for clinical study and

literature cases, only those judged not related to the drug by both the reporter and the manufacturer/sponsor should be excluded.

Reports of lack of efficacy specifically for drugs used in the treatment of life-threatening conditions, may represent a significant hazard, and in that sense be a "safety issue". Although these types of cases should not be included with the usual ADR presentations (i.e., line-listings and summary tabulations), such findings should be discussed within the PSUR (*see*: section 2.8), if deemed medically relevant.

Increase in the frequency of reports for known ADRs has traditionally been considered as relevant new information. Although attention should be given in the PSUR to such increased reporting, no specific quantitative criteria or other rules are recommended. Judgement should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile and whether an explanation can be proposed for such a change(e.g., population exposed, duration of exposure).

1.4.3 Products manufactured and/or marketed by more than one company
Each MAH is responsible for submitting PSURs, even if different companies market the same product in the same country. When companies are involved in contractual relationships (e.g., licensor-licensee), arrangements for sharing safety information should be clearly specified. In order to ensure that all relevant data will be duly reported to appropriate regulatory authorities, respective responsibilities for safety reporting should also be clearly specified.

When data received from a partner company(ies) might contribute meaningfully to the safety analysis and influence any proposed or effected changes in the reporting company's product information, these data should be included and discussed in the PSUR, even if it is known that they are included in another company's PSUR.

1.4.4 International birthdate and frequency of review and reporting
Each medicinal product should have as an International Birth Date (IBD), the date of the first marketing authorization for the product granted to any company in any country in the world. For administrative convenience, if desired by the MAH, the IBD can be designated as the last day of the same month. When a report contains information on different dosage forms, formulations, or uses (indications, routes, populations), the date of the first marketing authorization for any of the various authorizations should be regarded as the IBD and, therefore, determine the data lock point for purposes of the unified PSUR. The data lock point is the date designated as the cut-off for data to be included in a PSUR.

The need for a report and the frequency of report submission to authorities are subject to local regulatory requirements. The age of a drug on the market may influence this process.

In addition, during the initial years of marketing, a drug will ordinarily receive authorizations at different times in different countries; it is during this early period that harmonization of reporting is particularly important.

However, independent of the required reporting frequency, regulatory authorities should accept six-monthly PSURs or PSURs based on multiples of six months. Therefore, preparation of PSURs for all regulatory authorities should be based on data sets of six months or multiples thereof.

Once a drug has been marketed for several years, the need for a comprehensive PSUR and the frequency of reporting may be reviewed, depending on local regulations or requests, while maintaining one IBD for all regulatory authorities. In addition, approvals beyond the initial one for the active substance may be granted for new indications, dosage forms, populations, or prescription status (e.g., children vs. adults; prescription to non-prescription status). The potential consequences on the safety profile raised by such new types and extent of population exposures should be discussed between regulatory authorities and MAH since they may influence the requirements for periodic reporting.

The MAH should submit a PSUR within 60 days of the data lock point.

1.4.5 Reference safety information

An objective of a PSUR is to establish whether information recorded during the reporting period is in accord with previous knowledge on the drug's safety, and to indicate whether changes should be made to product information. Reference information is needed to perform this comparison. Having one reference source of information in common for the three ICH regions would facilitate a practical, efficient and consistent approach to the safety evaluation and make the PSUR a unique report accepted in all areas.

It is a common practice for MAHs to prepare their own "Company Core Data Sheet"(CCDS) which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the product. A practical option for the purpose of periodic reporting is for each MAH to use, as a reference, the safety information contained within its central document (CCDS), which will be referred to as "Company Core Safety Information" (CCSI).

For purposes of periodic safety reporting, CCSI forms the basis for determining whether an adverse drug reaction is already Listed or is still Unlisted, terms which are introduced to distinguish them from the ususal terminology of "expectedness" or "labeledness" which is used in association with official labeling. Thus, the local approved product information continues to be the reference document upon which labeledness/expectedness is based for the purpose of local expedited post-marketing safety reporting.

1.4.6 Presentation of data on individual case histories

Sources of information

Generally, data from the four following sources of ADR case information are potentially available to a MAH and should be included in the PSUR:

a) Direct reports to MAH (or under MAH control):
- **Spontaneous notifications from health care professionals**
- **Spontaneous notifications from non-health care professionals or from consumers (non-medically substantiated)**
- **MAH-sponsored clinical studies[42] or named-patient ("compassionate") use**

b) Literature

c) ADR reporting systems of regulatory authorities

d) Other sources of data:
- **reports on ADRs exchanged between contractual partners (e.g., licensors, licensees)**
- **data in special registries, such as maintained in organ toxicity monitoring centers reports created by poison control centers**
- **epidemiologic data bases**

Description of the reaction

Until an internationally agreed ICH coding terminology becomes available and its use broadly implemented, the event terms used in the PSUR will generally be derived from whatever standard terminology ("controlled vocabulary" or "coding dictionary") is used by the reporting company

Whenever possible, the notifying reporter's event terms should be used to describe the ADR. However, when the notifying reporter's terms are not medically appropriate or meaningful, MAHs should use the best alternative compatible event terms from their ADR dictionaries to ensure the most accurate representation as possible of the original terms. Under such circumstances, the following should be borne in mind:

- in order to make available on request, the "verbatim" information supplied by the notifying reporter should be kept on file (in the original language and/or as a medically sound English translation, if applicable)

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42 What constitutes a clinical study may not always be clear, given the recent use of, for example, stimulated reporting and patient-support programs. In some of these circumstances, the distinction between spontaneous reporting and a clinical study is not well defined. The MAH should specify how relevant data from such sources are included.

- in the absence of a diagnosis by the reporting health-care professional, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe a case, in addition to presenting the reported individual signs, symptoms and laboratory data

- if a MAH disagrees with a diagnosis by the reporting health-care professional, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe a case, in addition to presenting the reported individual signs, symptoms and laboratory data.

- MAH should report and try to understand all information provided within a case report. An example is a laboratory abnormality not addressed/evaluated by the notifying reporter.

Therefore, when necessary and relevant, two descriptions of the signs, symptoms or diagnosis could be presented in the line listing: first, the reaction as originally reported; second, when it differs, the MAH's medical interpretation (identified by asterisk or other means).

Line listings and/or summary tabulations

Depending on their type or source, available ADR cases should be presented as individual case line listings and/or as summary tabulations.

A line listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help regulatory authorities identify cases which they might wish to examine more completely by requesting full case reports.

MAHs can prepare line listings of consistent structure and content for cases directly reported to them (or under their control) (*see*: section 1.4.6a) as well as those received from regulatory authorities. They can usually do the same for published cases (ordinarily well documented; if not, follow-up with the author may be possible). However, inclusion of individual cases from second- or third-hand sources, such as contractual partners and special registries (*see*: section 1.4.6d) might not be (1) possible without standardization of data elements, or (2) appropriate due to the paucity of information, and might represent unnecessary re-entry/reprocessing of such information by the MAH. Therefore, summary tabulations or possibly a narrative review of these data are considered acceptable under these circumstances.

In addition to individual case line listings, summary tabulations of ADR terms for signs, symptoms and diagnoses across all patients should usually be presented to provide an overview. Such tabulations should be based on the data in line listings (e.g., all serious

ADRs and all non-serious unlisted ADRs), but also on other sources for which line listings are not requested (e.g., non–serious listed ADRs). Details are found in section 2.6.4.

2. MODEL FOR A PERIODIC SAFETY UPDATE REPORT (PSUR)

The following sections are organized as a sample PSUR. In each of the sections, guidance is provided on what should be included.

SAMPLE TITLE PAGE

PERIODIC SAFETY UPDATE REPORT FOR: (PRODUCT)

MAHs NAME AND ADDRESS (Corporate headquarters or other company entity responsible for report preparation)

PERIOD COVERED BY THIS REPORT: (dates)

INTERNATIONAL BIRTH DATE: Date (Country of IBD)

DATE OF REPORT

(Other identifying information at the option of MAH, such as report number)

TABLE OF CONTENTS FOR MODEL PSUR

Introduction

World-wide market authorization status

Update of regulatory authority or MAH actions taken for safety reasons

Changes to Reference Product Information

Patient exposure

Presentation of individual case histories .

Studies

Other information.

Overall safety evaluation

Conclusion

APPENDIX: COMPANY CORE DATA SHEET.

2.1 Introduction

The MAH should briefly introduce the product so that the report "stands alone" but is also placed in perspective relative to previous reports and circumstances.

Reference should be made not only to product(s) covered by the report but also those excluded. Exclusions should be explained; for example, they may be covered in a separate report (e.g., for a combination product).

If it is known that a PSUR on the same product(s) will be submitted by another MAH, some of whose data are included in the report (*see*: section 1.4.6), the possibility of data duplication should be noted.

2.2 World-wide Market Authorization Status

This section of the report provides cumulative information.

Information should be provided, usually as a table, on all countries in which a regulatory decision about marketing has been made related to the following:

- dates of market authorization, and subsequent renewal;

- any qualifications surrounding the authorization, such as limits on indications if relevant to safety;

- treatment indications and special populations covered by the market authorization, when relevant

- lack of approval, including explanation, by regulatory authorities;

- withdrawal by the company of a license application submission if related to safety or efficacy

- dates of launch when known

- trade name(s).

Typically, indications for use, populations treated (e.g., children vs. adults) and dosage forms will be the same in many or even most countries where the product is authorized. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the newly reported safety information that are related to such

different exposures. If more convenient and useful, separate regulatory status tables for different product uses or forms would be considered appropriate.

Country entries should be listed in chronological order of regulatory authorizations. For multiple authorizations in the same country (e.g., new dosage forms), the IBD for the active substance and for all PSURs should be the first (initial) authorization date.

Table 1 is an example, with fictitious data for an antibiotic, of how a table might be organized. The drug was initially developed as a solid oral dosage form for outpatient treatment of various infections.

2.3 Update of Regulatory Authority or MAH Actions Taken for Safety Reasons

This section should include details on the following types of actions relating to safety that were taken during the period covered by the report and between data lock-point and report submission:

- marketing authorization withdrawal or suspension
- failure to obtain a marketing authorization renewal
- restrictions on distribution
- clinical trial suspension
- dosage modification
- changes in target population or indications
- formulation changes.

The safety related reasons that led to these actions should be described and documentation appended when appropriate; any communication with the health profession (e.g., Dear Doctor letters) as a result of such action should also be described with copies appended.

2.4 Changes to Reference Safety Information

The version of the company core data sheet (CCDS) with its company core safety information (CCSI) in effect at the beginning of the period covered by the report should be used as the reference. It should be numbered, dated and appended to the PSUR and include the date of last revision.

Changes to the CCSI, such as new contraindications, precautions, warnings, ADRs, or interactions, already made during the period covered by the report, should be clearly described, with presentation of the modified sections. The revised CCSI should be used as the reference for the next report and the next period.

With the exception of emergency situations, it may take some time before intended modifications are introduced in the product-information materials provided to prescribers, pharmacists and consumers. Therefore, during that period the amended reference

document (CCDS) may contain more "listed" information than the existing product information in many countries.

When meaningful differences exist between the CCSI and the safety information in the official data sheets/product information documents approved in a country, a brief comment should be prepared by the company, describing the local differences and their consequences on the overall safety evaluation and on the actions proposed or initiated. This commentary may be provided in the cover letter or other addendum accompanying the local submission of the PSUR.

2.5 Patient Exposure

Where possible, an estimation of accurate patient exposure should cover the same period as the interim safety data. While it is recognized that it is usually difficult to obtain and validate accurate exposure data, an estimate of the number of patients exposed should be provided along with the method used to derive the estimate. An explanation and justification should be presented if the number of patients is impossible to estimate or is a meaningless metric. In its place, other measures of exposure, such as patient-days, number of prescriptions or number of dosage units are considered appropriate; the method used should be explained. If these or other more precise measures are not available, bulk sales (tonnage) may be used. The concept of a defined daily dose may be used in arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially pediatric vs. adult) should be provided.

When a pattern of reports indicates a potential problem, details by country (with locally recommended daily dose) or other segmentation (e.g., indication, dosage form) should be presented if available.

When ADR data from clinical studies are included in the PSUR, the relevant denominator(s) should be provided. For ongoing and/or blinded studies, an estimation of patient exposure may be made.

2.6 Presentation of Individual Case Histories

2.6.1 General considerations

Follow-up data on individual cases may be obtained subsequent to their inclusion in a PSUR. If such information is relevant to the interpretation of the case (e.g., significant impact on the case description or analysis), the new information should be presented in the next PSUR, and the correction or clarification noted relative to the earlier case description.

With regard to the literature, MAHs should monitor standard, recognized medical and scientific journals for safety information on their products and/or make use of one or more literature search/summary services for that purpose. Published cases may also have been received as spontaneous cases, be derived from a sponsored clinical study, or arise from other sources. Care should be taken to include such cases only once. Also, no matter what

"primary source" is given a case, if there is a publication, it should be noted and the literature citation given.

In some countries, there is no requirement to submit medically unconfirmed spontaneous reports that originate with consumers or other non-health care professionals. However, such reports are acceptable or requested in other countries. Therefore, medically unconfirmed reports should be submitted as addenda line listings and/or summary tabulations only when requested by regulatory authorities. However, it is considered that such reports are not expected to be discussed within the PSUR itself.

2.6.2 Cases presented as line listings

The following types of cases should be included in the line listings (Table 2); attempts should be made to avoid duplicate reporting of cases from the literature and regulatory sources.

- all serious reactions, and non-serious unlisted reactions, from spontaneous notifications

- all serious reactions (attributable to drug by either investigator or sponsor), available from studies or named-patient ("compassionate") use

- all serious reactions, and non-serious unlisted reactions, from the literature

- all serious reactions from regulatory authorities

Collection and reporting of non-serious, listed ADRs may not be required in all ICH countries. Therefore, a line listing of spontaneously reported non-serious listed reactions that have been collected should be submitted as an addendum to the PSUR only when requested by a regulatory authority.

2.6.3 Presentation of the line listing

The line listing(s) should include each patient only once regardless of how many adverse event/reaction terms are reported for the case. If there is more than one event/reaction, they should all be mentioned but the case should be listed under the most serious ADR (sign, symptom or diagnosis), as judged by the MAH. It is possible that the same patient may experience different ADRs on different occasions (e.g., weeks apart during a clinical trial). Such experiences would probably be treated as separate reports. Under such circumstances, the same patient might then be included in a line-listing more than once, and the linelistings should be cross-referenced when possible. Cases should be organized (tabulated) by body system (standard organ system classification scheme).

The following headings should usually be included in the line listing:

- MAH case reference number

- Country in which case occurred

- Source (e.g., clinical trial, literature, spontaneous, regulatory authority)

- Age and sex

- Daily dose of suspected drug (and, when relevant, dosage form or route)

- Date of onset of the reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in Comments section).

- Dates of treatment. If not available, best estimate of treatment duration.

- Description of reaction as reported, and when necessary as interpreted by the MAH (English translation when necessary). See section 1.4.6 for guidance.

- Patient outcome (at case level) (e.g., resolved, fatal, improved, sequelae, unknown). This field does not refer to the criteria used to define a "serious" ADR. It should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.

- Comments, if relevant (e.g., causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available).

Depending on the product or circumstances, it may be useful or practical to have more than one line listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

2.6.4 Summary tabulations

An aggregate summary for each of the line listings should usually be presented. These tabulations ordinarily contain more terms than patients. It would be useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g., by source of report). See Table 3 for a sample data presentation on serious reactions.

A summary tabulation should be provided for the non-serious, listed, spontaneously reported reactions (*see*: section 2.6.2).

The terms used in these tables should ordinarily be those used by the MAH to describe the case (*see*: section 1.4.6).

Except for cases obtained from regulatory authorities, the data on serious reactions from Other Sources (*see*: section 1.4.6c) should normally be presented only as a summary tabulation. If useful, the tabulations may be sorted by source of information or country, for example.
When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description rather than a formal table is considered suitable.

As previously described, the data in summary tabulations should be interval data, as should the line-listings from which they are derived. However, for ADRs that are both serious and unlisted, a cumulative figure (i.e., all cases reported to date) should be provided in the table(s) or as a narrative.

2.6.5 MAH, Analysis of Individual Case Histories
This section may be used for brief comments on the data concerning individual cases. For example, discussion can be presented on particular serious or unanticipated findings (their nature, medical significance, mechanism, reporting frequency, etc.). The focus here should be on individual case discussion and should not be confused with the global assessment in the Overall Safety Evaluation (*see*: section 2.9).

2.7 Studies
All completed studies (non-clinical, clinical, epidemiological) yielding safety information with potential impact on product information, studies specifically planned or in progress, and published studies that address safety issues, should be discussed.

2.7.1 Newly analyzed company-sponsored studies
All relevant studies containing important safety information and newly analyzed during the reporting period should be described, including those from epidemiological, toxicological or laboratory investigations. The study design and results should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to non-clinical and clinical study reports. Copies of full reports should be appended only if deemed appropriate.

2.7.2 Targeted new safety studies planned, initiated or continuing during the reporting period.

New studies specifically planned or conducted to examine a safety issue (actual or hypothetical) should be described (e.g., objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented. When the study is completed and analyzed, the final results should be presented in a subsequent PSUR as described under section 2.7.1.

2.7.3 Published safety studies
Reports in the scientific and medical literature, including relevant published abstracts from meetings, containing important safety findings (positive or negative) should be summarized and publication reference(s) given.

2.8 Other Information
2.8.1 Efficacy-Related Information
For a product used to treat serious or life threatening diseases, medically relevant lack of efficacy reporting, which might represent a significant hazard to the treated population, should be described and explained.

2.8.2 Late-Breaking Information
Any important, new information received after the data base was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important follow-up data. These new data should be taken into account in the Overall Safety Evaluation (*see:* section 2.9).

2.9 Overall Safety Evaluation
A concise analysis of the data presented, taking into account any late-breaking information (*see:* section 2.8.2.), and followed by the MAH assessment of the significance of the data collected during the period and from the perspective of cumulative experience should highlight any new information on:

- a change in characteristics of listed reactions, e.g. severity, outcome, target population

- serious unlisted reactions, placing into perspective the cumulative reports

- non-Serious unlisted reactions

- an increased reporting frequency of listed reactions, including comments on whether it is believed the data reflect a meaningful change in ADR occurrence.

The report should also explicitly address any new safety issue on the following (lack of significant new information should be mentioned for each):

- drug interactions

- experience with overdose, deliberate or accidental, and its treatment

- drug abuse or misuse

- positive or negative experiences during pregnancy or lactation
- experience in special patient groups (e.g., children, elderly, organ impaired)

- effects of long-term treatment.

2.10 Conclusion
The conclusion should:

- indicate which safety data do not remain in accord with the previous cumulative experience, and with the reference safety information (CCSI);

- specify and justify any action recommended or initiated.

APPENDIX: COMPANY CORE DATA SHEET

The Company Core Data Sheet in effect at the beginning of the period covered should be appended to the PSUR.

3. GLOSSARY OF SPECIAL TERMS

Company Core Data Sheet (CCDS)
A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.

Company Core Safety Information (CCSI)
All relevant safety information contained in the Company Core Data Sheet prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Data Lock-Point (Data Cut-off Date)
The date designated as the cut-off date for data to be included in a PSUR. It is based on the International Birth Date (IBD) and should usually be in six-monthly increments.

International Birth Date (IBD)
The date of the first marketing authorization for a new medicinal product granted to any company in any country in the world.

Listed Adverse Drug Reaction
An ADR whose nature, severity, specificity, and outcome are consistent with the information in the CCSI.

Spontaneous Report or Spontaneous Notification
An unsolicited communication to a company, regulatory authority or other organization that describes an adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study or any organized data collection scheme.

Unlisted Adverse Drug Reaction
An ADR whose nature, severity, specificity or outcome are not consistent with the information included in the CCSI.

- Table 1 -

EXAMPLE OF PRESENTATION OF WORLD WIDE MARKET AUTHORIZATION STATUS

Country	Action Date	Launch Date	Trade Name(s)	Comments
Sweden	A-7/90 AR-10/95	12/90 -	Bacteroff -	- -
Brazil	A-10/91 A-1/93	2/92 3/93	Bactoff Bactoff - IV	- IV dosage form
United Kingdom	AQ-3/92 A-4/94	6/92 7/94	Bacgone Bacgone-C (skin infs)	Elderly (>65) excluded (PK) Topical cream
Japan	LA-12/92	-	-	to be refiled
France	V-9/92	-	-	Unrelated to safety
Nigeria	A-5/93 A-9/93	7/93 1/94	Bactoff Bactoff	- -
Etc.				

Abbreviations for Action: A= authorized; AQ=authorized with qualifications; LA lack of approval; V=voluntary marketing application withdrawal by company; AR=Authorization renewal

- Table 2 -

PRESENTATION OF INDIVIDUAL CASE HISTORIES

(*see*: sections 2.6.2 and 2.6.4 for full explanation)

Source	Type of Case	Only Summary Tabulation	Line Listing and Summary Tabulation
1. Direct Reports to MAH			
- spontaneous ADR reports*	S	-	+
	NS U	-	+
	NS L**	+	-
- MAH sponsored studies	SA	-	-
2. Literature	S	-	+
	NS U	-	+
3. Other sources			
- regulatory authorities	S	-	+
- contractual partners	S	+	-
- registries	S	+	-

** Medically unconfirmed reports should be provided as a PSUR addendum only on request by regulatory authorities, as a line listing and/or summary tabulation.*

*** Line listing shoud be provided as PSUR addendum only on request by regulatory authorities.*

S=serious; L=listed; A=attributable to drug (by investigator or sponsor); NS=non-serious; U=Unlisted

-Table 3 -

(EXAMPLE OF SUMMARY TABULATION)#
NUMBER OF REPORTS BY TERM (SIGNS, SYMPTOMS AND DIAGNOSES) FROM SPONTANEOUS (MEDICALLY CONFIRMED), CLINICAL STUDY AND LITERATURE
CASES: ALL SERIOUS REACTIONS

(An * indicates an unlisted term)

Body system/ ADR term	Spontaneous/ Regulatory bodies	Clinical trials	Literature
CNS hallucinations*	2	0	0
etc.			
etc.			
Sub-total			
CV			
etc.			
etc.			
Sub-total			
Etc.			
Total			

In a footnote (or elsewhere), the number of patient-cases that represent the tabulated terms might be given (e.g., x-spontaneous/regulatory, y-clinical study, and z-literature cases)

 # This table is only one example of different possible data presentations which are at the discrtion of the MAH (e.g., serious and non-serious in the same table or as separate tables, etc.)

APPENDIX 5:

International Comparison of Post Approval Requirements for Product Safety Reporting

International Comparison of Post Approval Requirements for Safety Reporting*

	United St		Europe		Canada	
	Current			Within ICH		Within PLF
Type of Report	Safety	PSUR	Safety	PSUR	ADR Report	PSUR
	•summary & analysis of serious & unexpected reports •line listing of other reports •history of Adverse Event related actions •new clinical & toxicology studies	•content & format as per ICH document direction	•detailed record of all suspected Adverse Events •scientific /clinical safety evaluation	•content & format as per ICH document direction	•summary line listing of all ADRs •critical analysis •evaluation and any recommended actions	•content & format as per ICH document direction
Frequency of Reporting	•quarterly for 3 years •annually thereafter	•decision not final	•varies country to country	•every 6 months for 2 years •annually for 3 years •summary report every 5 years	•prepare annually for all products •submit on request	Schedule A •prepare & submit every 6 mos. for 2 years •summary report at 2 years Schedule B •prepare & submit annually for 3 years •submit summary report at 3 years Schedule C •as per current ADR requirements

** table does not address expedited reporting required in all jurisdictions*

APPENDIX 6:

Glossary of Terms

Glossary of Terms

Active Substance - the substance which produces the therapeutic effect and which is usually formulated with excipients and processed in some way to yield a drug product. Also known as medicinal substance or drug substance, active raw material or bulk pharmaceutical substance, bulk pharmaceutical compound and bulk pharmaceutical raw material.

Adverse Drug Reaction - a response to a drug which is noxious and unintended and which occurs at doses normally used or tested in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function.

Domestic Adverse Drug Reaction - an adverse drug reaction which occurs in Canada.

Foreign Adverse Drug Reaction - an adverse drug reaction occurring outside of Canada.

Serious Adverse Drug Reaction - a noxious and unintended response to a drug which occurs at any dose and requires in-patient hospitalization, prolongation of existing hospitalization, causes congenital malformatin, results in persistent or significant disability or incapacity, is life-threatening or results in death.

Serious Unexpected Adverse Drug Reaction - a serious adverse drug reaction that is not identified in nature, severity, or frequency in the risk information set out on the label of the drug

Bioavailability - the rate and extent of absorption of a drug into the systemic circulation.

Bioequivalence - a high degree of similarity in the bioavailabilities of two pharmaceutical products (of the same galenic form) from the same molar dose, that are unlikely to produce clinically relevant differences in therapeutic effects, or adverse effects, or both.

Biological - a drug derived from living organisms ranging from normal or genetically modified microorganisms to fluids and tissues derived from various animal and human sources. *(World Health Organization)*

Biopharmaceutics List - a list of drug products for which the Therapeutic Products Programme has bioavailability or pharmaceutical chemistry concerns.

Dosage Form - the pharmaceutical form in which a drug product is sold by a drug manufacturer.

Drug Product - the dosage form in the final immediate packaging intended for marketing by a specific drug manufacturer.

Formulation - an ingredient or mixture of specfic ingredients; that is, drug substances and non-medicinal ingredients in specific amounts, defining a given product.

Indication for Use - the condition for which a drug product is approved for treatment.

International Conference on Harmonization (ICH) - an initiative that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of drug product registration. The objective is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for drug product registration. Canada is an observer to the ICH process.

Labelling - includes any legend, work, or mark attached to, included in, belonging to, or accompanying, any food, drug, cosmetic, device, or package.

Licence - a notification to the drug product sponsor that a drug product has been approved for use in Canada by the Therapeutic Products Programme. The licence will stipulate the post-approval reporting schedule assigned to the drug product.

Modified-release dosage form - a drug formulation that differs from conventional formulations in the rate at which the drug is released.

New Active Substance - includes:

- **a chemical, plant or biological substance not previously licensed for sale as a drug in Canada; or,**
- **an derivative, isomer or salt of a chemical substance previously licensed for sale as a drug in Canada but differing in properties with regard to safety and/or efficacy; or,**
- **a biological substance previously licensed for sale as a drug in Canada, which differs in molecular structure, nature of the source material or manufacturing process, and differing in properties with regard to safety and/or efficacy from than previously licensed biological substance.**

Non-Medicinal Ingredient - any substance, other than a medicinal ingredient, added to a drug product in the course of its manufacture and present in the dosage form in which the drug product is to be sold.

Periodic Safety Update Report (PSUR) - a report which provides information on the world-wide safety experience with an active substance at specific times following its approval for

use. The format and content of this report has been agreed upon by the International Conference on Harmonization.

Pharmaceutical equivalence - the condition in which drug products contain identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that do not necessarily contain the same non-medicinal ingredients, and meet a compendial and/or other applicable standard of identity, strength, quality, purity and potency.

Radiopharmaceutical - a drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons.

Radiopharmaceutical kit - a package that contains one or more separately packaged units of a drug, other than a radionuclide and that may contain empty vials or other accessory items, for use in the preparation of radiopharmaceuticals.

Route of administration - method whereby a drug is introduced into the body, i.e. oral ingestion, topical application, intravenous injection, etc.

Schedule F - a schedule to the Food and Drug Regulations which lists ingredients for which a prescription is required before a drug product containing that ingredient can be sold. Part I of Schedule F lists ingredients that require a prescription both for human and veterinary use. Part II lists ingredients that require a prescription for human use but not for veterinary use.

Special Access Program (SAP) - formerly the Emergency Drug Release Program (EDRP), the Special Access Program (SAP) provides for the release of drugs which are otherwise unavailable for sale in Canada, to physicians, dentists and veterinarians. Through SAP, the Therapeutic Products Programme provides legal access to these drugs; however, it does not endorse their safety. Practitioners who use the program must agree to report on the outcome of the therapy with the drug, including any adverse reactions.

Sponsor - a person that, under his own name, or under a trade, design or word mark, trade name, or other name, word or mark controlled by him, sells a drug product. "Person" in this context includes firms, partnerships and corporations.

Subsequent Entry Product - also known as a "generic" or "second-entry" product.